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CMH Clinical and Molecular Hepatology

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

The 25th Annual Meeting of the Korean Association for the Study of the Liver
The Korean Association of HBP Surgery Symposium
The 22nd General Symposium of the Korean Liver Cancer Association
The Korean Liver Transplantation Society Symposium

The Korean Association for the Study of the Liver
THE KOREAN ASSOCIATION OF HBP SURGERY
THE KOREAN LIVER CANCER ASSOCIATION
The Korean Liver Transplantation Society

WELCOME MESSAGE

Dear colleagues,

On behalf of all the organizing committee members, we sincerely welcome you to The Liver Week 2019.

Since the first meeting was held in 2014, The Liver Week has become a multidisciplinary international conference hosted by the Korean Association for the Study of the Liver (KASL), in partnership with three co-hosting societies: the Korean Association of HBP Surgery (KAHBPS), the Korean Liver Cancer Association (KLCA), and the Korean Liver Transplantation Society (KLTS).

The theme of The Liver Week 2019, 'Expanding Frontiers in Liver Diseases', pursues the objectives of encouraging all participants to study the recent research trends and views related to liver disorders from the perspectives of eminent experts, and of facilitating the exchange of up-to-date information on liver disease with the ultimate goal of improving liver disease management. The organizing committee has prepared an attractive and valuable scientific program focused on the latest trends, issues, and advances made in various areas of liver diseases.

In particular, we have prepared various joint symposia for exchanging knowledge among 4 liver-related societies. The experts debate session will cover an issue regarding cessation of anti-HBV therapy. The Korea Center for Disease Control and Prevention (KCDC) will participate in the policy forum, and the National Health Insurance Big Data Research forum will also be held in partnership with the National Health Insurance Service (NHIS). Lectures and a hands-on course for abdominal ultrasound specialist certification and relevant major education are prepared as well. The Asian Forum is a new session covering current status and emerging liver disease issues in Asia.

We firmly believe that The Liver Week 2019 will be a valuable experience for all attendees and we look foward to your active participation.

Thank you.

Jin Mo Yang
President
The Liver Week 2019

Kwan Sik Lee
Chairman
The Liver Week 2019

Hee Chul Yu
Vice President
The Liver Week 2019

Seung Kew Yoon
Vice President
The Liver Week 2019

Myoung Soo Kim
Vice President
The Liver Week 2019

The Korean Association for the Study of the Liver

THE KOREAN ASSOCIATION OF HBP SURGERY

THE KOREAN LIVER CANCER ASSOCIATION

The Korean Liver Transplantation Society

PROGRAM AT A GLANCE

DAY 1 Thursday, June 20, 2019

K: Session in Korean

POSTGRADUATE COURSE *" Diagnosis and Management of Liver Disease: Past, Present, and Future"*

Course Director's Message

Moon Young Kim, Yonsei University Wonju

The Postgraduate Course is prepared to be a practical help for the participants in the treatment of various liver diseases by organizing the parts that are often encountered in the clinical field but have not been dealt with systematically so far. In addition, we have focused on introducing new concepts and preparing ourselves for changes in the future of liver diseases in areas that have recently been newly defined and are growing in scope.

ROOM A [1F] 102-105 / 107-110

K: Session in Korean

08:50-10:30	**PG 1. Viral Hepatitis** (*K)	*Seong Gyu Hwang (CHA Univ.), Hong Soo Kim (Soonchunhyang Univ.)*
08:50-09:15	Anti-Hepatitis B Virus Therapy in Special Population	*Jeong-Hoon Lee (Seoul National Univ.)*
09:15-09:40	Anti-Hepatitis C Virus Therapy in Real-World Practice	*Geum-Youn Gwak (Sungkyunkwan Univ.)*
09:40-10:05	Hepatitis E Virus: Epidemiology, Diagnosis, and Management	*Nae-Yun Heo (Inje Univ.)*
10:05-10:30	Future Hepatitis B Virus Therapy	*Jung Hyun Kwon (The Catholic Univ. of Korea)*
10:30-10:50	Coffee Break	
10:50-12:30	**PG 2. Cirrhosis and Its Complications** (*K)	*Byung Ik Kim (Sungkyunkwan Univ.), Chang Hyeong Lee (Daegu Catholic Univ.)*
10:50-11:15	Covert and Overt Hepatic Encephalopathy	*Sang Gyune Kim (Soonchunhyang Univ.)*
11:15-11:40	Frailty and Sarcopenia in Cirrhosis	*Seung Up Kim (Yonsei Univ.)*
11:40-12:05	Interventional Treatment of Varices: TIPS, BRTO, and PARTO	*Dongho Hyun (Sungkyunkwan Univ.)*
12:05-12:30	Sepsis in Cirrhosis: New Definition and Application	*Dae Hee Choi (Kangwon National Univ.)*
12:30-13:30	Luncheon Symposium 1 [Abbvie]	
13:30-13:50	Coffee Break	
13:50-15:30	**PG 3. Alcohol-Related and Non-Alcoholic Fatty Liver Disease** (*K)	*Yung Sang Lee (Univ. of Ulsan), Youn-Jae Lee (Inje Univ.)*
13:50-14:15	Alcoholic Hepatitis from 1971 to 2019	*Soung Won Jeong (Soonchunhyang Univ.)*
14:15-14:40	Update on Imaging and Serum Biomarkers of Non-Alcoholic Fatty Liver Disease	*Won Kim (Seoul National Univ.)*
14:40-15:05	Real Treatment Target of Non-Alcoholic Fatty Liver Disease: Steatosis vs. Fibrosis	*Dae Won Jun (Hanyang Univ.)*
15:05-15:30	Metabolic Syndrome in Non-Alcoholic Fatty Liver Disease from Hepatologist's Perspective	*Yang Hyon Baek (Dong-A Univ.)*
15:30-15:50	Coffee Break	
15:50-17:30	**PG 4. Liver Tumors** (*K)	*Chang Min Kim (National Cancer Center), Kyung Sik Kim (Yonsei Univ.)*
15:50-16:15	Radiologic Assessment of Hepatic Nodules	*Jin-Young Choi (Yonsei Univ.)*
16:15-16:40	Surveillance of Hepatocellular Carcinoma: Risk Stratification	*Sung Bum Cho (Chonnam National Univ.)*
16:40-17:05	Clinical Decision of Surgical Management: Benign Lesions	*Sae Byeol Choi (Korea Univ.)*
17:05-17:30	Clinical Decision of Surgical Management: Hepatocellular Carcinoma and Cholangiocarcinoma	*Gi-Won Song (Univ. of Ulsan)*

ROOM D [2F] 205

K: Session in Korean

10:50-12:30	**Basic Forum 1. Hepatitis Virus** (*K)	*Soon Bong Hwang (Chonbuk National Univ.), Jin-Wook Kim (Seoul National Univ.)*
10:50-11:15	Molecular Basis for Cure of Hepatitis B Virus Infection	*Kyun-Hwan Kim (Konkuk Univ.)*
11:15-11:40	Drug Development for Hepatitis B Virus Treatment	*Sung-Gyoo Park (GIST)*
11:40-12:05	Identification and Validation of Druggable Targets in the Hepatitis C Virus Life Cycle	*Soon Bong Hwang (Chonbuk National Univ.)*
12:05-12:30	Hepatitis C Virus Vaccine Development	*Eui-Cheol Shin (KAIST)*
12:30-13:30	Luncheon Symposium 2 [Il-dong]	
13:30-13:50	Coffee Break	
13:50-15:30	**Basic Forum 2. Hepatocellular Carcinoma and Steatohepatitis** (*K)	*Sang Hoon Park (Hallym Univ.), Yong-Han Paik (Sungkyunkwan Univ.)*
13:50-14:15	Understanding of Immune Checkpoint Inhibitors in Hepatocellular Carcinoma	*Su-Hyung Park (KAIST)*
14:15-14:40	Hepatocarcinogenesis and Animal Model	*Weonsang Ro (Yonsei Univ.)*
14:40-15:05	Hepatic mGluR5 Signaling in Endocannabinoid-Mediated Alcoholic Steatosis	*Won-il Jeong (KAIST)*
15:05-15:30	Pathogenesis of Non-Alcoholic Steatohepatitis	*Sang Geon Kim (Seoul National Univ.)*
15:30-15:50	Coffee Break	
15:50-17:30	**Research Consortium Forum** (*K)	*Sung Kyu Choi (Chonnam National Univ.), Young Oh Kweon (Kyungpook National Univ.)*
15:50-16:00	Gangwon Branch	*Minjong Lee (Gangwon National Univ.)*
16:00-16:10	Gyeonggi-Incheon Branch	*Jeong-Ju Yoo (Soonchunhyang Univ.)*
16:10-16:20	Gwangju-Jeonnam Branch	*Chung Hwan Jun (Chonnam National Univ.)*
16:20-16:30	Daegu-Kyungpook Branch	*Jung Gil Park (Yeungnam Univ.)*
16:30-16:40	Daejeon-Chungcheong Branch	*Suk Bae Kim (Dankook Univ.)*
16:40-16:50	Busan-Ulsan-Kyungnam Branch	*Nae-Yun Heo (Inje Univ.)*
16:50-17:00	Jeonbuk Branch	*Chang Hun Lee (Chonbuk National Univ.)*
17:00-17:10	Jeju Branch	*Young Nam Kim (Cheju Halla General Hospital)*
17:10-17:30	Discussion	

PROGRAM AT A GLANCE

DAY 2 Friday, June 21, 2019

K: Session in Korean

	[ROOM A]	[ROOM BC]	[ROOM D]	[ROOM E]	[ROOM A]	[ROOM B]	[ROOM C]	[ROOM D]	[ROOM E]	[ROOM F]
	103–105/108–110	101–102	106	107	201–202	203	204	205	206	207
07:00										
08:00			Early Morning Workshop (07:30-08:30)	Early Morning Workshop (07:30-08:30)						
09:00	Symposium 1. NAFLD/ALD (08:30-09:30)				KLTS Symposium 1 (08:30-09:30)			KLCA Symposium 1 (08:30-09:30)	Free Paper 1 HBV (08:30-09:30)	
	Coffee Break (09:30-09:50)									
10:00	Opening Ceremony									
11:00	Plenary Session 1 (10:10-11:10)									
12:00	Special Lectures with Debates (11:10-12:10)	Hepatology Associates Course (11:10-12:10) K	Health Policy Forum (11:10-12:10) K		KAHBPS-KLTS Joint Symposium (11:10-12:10)			KLCA General Meeting (11:10-12:10) K	Free Paper 2 ALD&NAFLD (11:10-12:10)	
13:00	Luncheon Symposium 3 [Gilead] (12:10-13:10)	Luncheon Symposium 4 [MSD] (12:10-13:10)			KLTS General Meeting & Luncheon Symposium 5 [Astellas] (12:10-13:10)			Luncheon Symposium 6 [Bayer] (12:10-13:10)		
	Break (13:10-13:30)									
14:00	State-of-the-Art Lecture 1 (13:30-14:00)				KLTS Special Lecture (13:30-14:00)		Free Paper 3 Liver Cancer, Basic (13:30-14:30)		Free Paper 4 Cirrhosis & Liver Failure (13:30-14:30)	
15:00	Symposium 2. HBV (14:00-15:30)		KCDC-KASL Joint Symposium (14:00-15:30) K	Satelite Symposium for Regeneration Medicine (14:00-15:40)	KLTS Symposium 2 (14:10-15:30) K	KLTS Coordinator Session (14:10-15:30) K		LCSGJ-KLCA Joint Symposium (13:30-15:30)	Free Paper 5 HCV (14:30-15:30)	
16:00	Poster Round (15:30-16:30)							Free Paper 6 Liver Cancer (15:30-16:30)		Press Forum (15:30-16:30) K
17:00	Clinical Hepatology Update (16:30-17:50) K				KASL-KLTS Joint Symposium (16:30-17:50) K	Free Paper 7 Surgery-Biliary (16:30-17:50)	Free Paper 8 Surgery-Technical Issues (16:30-17:50)	KLCA Symposium 2 (16:30-17:50)	Free Paper 9 ALD&NAFLD (16:30-17:50)	
18:00		Faculty Dinner @ Nurimaru [Invitation Only] (18:30-)								

The Korean Association for the Study of the Liver (KASL)
The Korean Liver Transplantation Society (KLTS)
The Korean Association of HBP Surgery (KAHBPS)
The Korean Liver Cancer Association (KLCA)
The Liver Cancer Study Group of Japan (LCSGJ)
Korea Centers for Disease Control & Prevention (KCDC)

ROOM A [1F] 103-105 / 108-110

K: Session in Korean

08:30-09:30	**Symposium 1. Non-Alcoholic Fatty Liver Disease and Alcohol-Related Liver Disease**	*Dong Joon Kim (Hallym Univ.), Yong Kyun Cho (Sungkyunkwan Univ.)*
08:30-08:50	Fecal Microbiota Transplant in Alcoholic Hepatitis	*SM Shasthry (Institute of Liver and Biliary Sciences, India)*
08:50-09:10	Systemic Manifestation in Non-Alcoholic Fatty Liver Disease	*Donghee Kim (Stanford Univ., USA)*
09:10-09:30	Update on the Management of Non-Alcoholic Fatty Liver Disease	*Vincent Wong (The Chinese Univ. of Hong Kong, Hong Kong)*
09:30-09:50	Coffee Break	
09:50-10:10	Opening Ceremony	
10:10-11:10	**Plenary Session 1**	*Joung Il Lee (Kyung Hee Univ.), Hee Jung Wang (Ajou Univ.), Jung-Hwan Yoon (Seoul National Univ.)*
11:10-12:10	**Special Lectures with Debates. Can We Discontinue Hepatitis B Virus Therapy? *Pros. vs. Cons.***	*Jordan Feld (Univ. of Toronto,Canada), Henry LY Chan (The Chinese Univ. of Hong Kong, Hong Kong)*
11:10-11:25	Nucleoside Analogue (NUC) Treatment Can Be Discontinued	*Chun-Jen Liu (National Taiwan Univ., Taiwan)*
11:25-11:40	NUC Treatment Should Be Continued	*Young-Suk Lim (Univ. of Ulsan)*
11:40-12:10	Panel Discussion	*Wai-Kay Seto (Univ. of Hong Kong, Hong Kong), Hyung Joon Yim (Korea Univ.)*
12:10-13:10	Luncheon Symposium 3 [Gilead]	
13:10-13:30	Break	
13:30-14:00	**State-of-the-Art Lecture 1**	*Dong Jin Suh (KMP Healthcare Seoul Clinic)*
13:30-14:00	Hepatitis B Virus: From Control to Cure	*Jia-Horng Kao (National Taiwan Univ., Taiwan)*
14:00-15:30	**Symposium 2. Hepatitis B Virus**	*Kwan Sik Lee (Yonsei Univ.), Jong Eun Yeon (Korea Univ.)*
14:00-14:20	Viral Factors for Hepatitis B Virus-Related Hepatocellular Carcinoma	*Jeong Won Jang (The Catholic Univ. of Korea)*
14:20-14:40	Novel Biomarkers in Management of Chronic Hepatitis B	*Yasuhito Tanaka (Nagoya City Univ., Japan)*
14:40-15:00	Current Treatment Strategy: Towards Hepatitis B Virus Cure	*Seng Gee Lim (National Univ. of Singapore, Singapore)*
15:00-15:20	Future Treatment Strategy: Towards Hepatitis B Virus Cure	*Henry LY Chan (The Chinese Univ. of Hong Kong, Hong Kong)*
15:20-15:30	Discussion	
15:30-16:30	Poster Round	**Grand Ballroom** [3F]
16:30-17:50	**Clinical Hepatology Update. Clinical Trials of Management in Chronic Liver Diseases** (*K)	*Kwang Cheol Koh (Sungkyunkwan Univ.), Il Han Song (Dankook Univ.)*
16:30-16:50	Chronic Hepatitis B: Where Are We Now for Functional Cure?	*Hyun Woong Lee (Yonsei Univ.)*
16:50-17:10	Non-Alcoholic Steatohepatitis: Key Targets and Endpoints	*Byoung Kuk Jang (Keimyung Univ.)*
17:10-17:30	Cirrhosis: Effort against Fibrosis and Portal Hypertension	*Kyung-Ah Kim (Inje Univ.)*
17:30-17:50	Hepatocellular Carcinoma Treatment Showdown: Mono vs. Combination Therapy	*Ju Hyun Shim (Univ. of Ulsan)*

ROOM BC [1F] 101-102

11:10-12:10	**Hepatology Associates Course** (*K)	*Byung Seok Lee (Chungnam National Univ.), Byung-Cheol Song (Jeju National Univ.)*
11:10-11:25	Treatment of Chronic Hepatitis B and C Virus	*Eileen L. Yoon (Inje Univ.)*
11:25-11:40	Management of Acute Variceal Bleeding	*Seung Kak Shin (Gachon Univ.)*
11:40-11:55	Liver Transplantation: When and How?	*Bum-Soo Kim (Kyung Hee Univ.)*
11:55-12:10	Hepatocellular Carcinoma: Diagnosis and Tumor Staging	*Woo Jin Chung (Keimyung Univ.)*

ROOM BC [1F] 101-102

K: Session in Korean

12:10-13:10	Luncheon Symposium 4 [MSD]	

ROOM D [1F] 106

07:30-08:30	**Early Morning Workshop 1. Meet the Professor: Cirrhosis**	*Rino Gani (Univ. of Indonesia, Indonesia), Sang Gyune Kim (Soonchunhyang Univ.)*
07:30-07:55	Management of Cirrhotic Complications: Guidelines and Real Experience	*C. Rinaldi A. Lesmana (Univ. of Indonesia, Indonesia)*
07:55-08:20	Key Summary of EASL Clinical Practice Guidelines for the Management of Patients with Decompensated Cirrhosis	*Paolo Angeli (Univ. of Padova, Italy)*
08:20-08:30	Discussion	
11:10-12:10	**Health Policy Forum: Policy Demand for Clinical Practice of Chronic Liver Disease** (*K)	*Young Seok Kim (Soonchunhyang Univ.), Moon Seok Choi (Sungkyunkwan Univ.)*
11:10-11:25	Exceptional Insurances in the Field of End-Stage Liver Disease	*Jeong Han Kim (Konkuk Univ.)*
11:25-11:40	Policy of KASL for Elimination of Hepatitis	*Sung-Eun Kim (Hallym Univ.)*
11:40-11:55	Liver Disease-Related Issue to Strengthen Health Insurance Coverage Expansion Policy	*Eun Sun Jang (Seoul National Univ.)*
11:55-12:10	Future Policy of Government for Administration of Chronic Liver Disease	*Young Ki Jeong (Ministry of Health and Welfare)*
14:00-15:30	**KCDC-KASL Joint Symposium** (*K)	*Youngmee Jee (Korea National Institute of Health), Sook-Hyang Jeong (Seoul National Univ.)*
14:00-14:20	Overview of Hepatitis Prevention and Control in the Republic of Korea	*Sung Won Lee (The Catholic Univ. of Korea)*
14:20-14:40	National Viral Hepatitis Control Program	*Hyerim Lee (Korea Centers for Disease Control and Prevention)*
14:40-14:55	Korea HBV Cohort Study	*Beom Kyung Kim (Yonsei Univ.)*
14:55-15:10	Korea HCV Cohort Study	*Eun Sun Jang (Seoul National Univ.)*
15:10-15:30	Discussion	

ROOM E [1F] 107

07:30-08:30	**Early Morning Workshop 2. Meet the Professor: Non-Alcoholic Fatty Liver Disease**	*Oidov Baatarkhuu (Mongolian National Medical Univ., Mongolia), Joo Hyun Sohn (Hanyang Univ.)*
07:30-07:50	Recent Epidemiology of Non-Alcoholic Fatty Liver Disease	*Donghee Kim (Stanford Univ., USA)*
07:50-08:10	Non-Alcoholic Fatty Liver Disease and Diabetes: Chicken or Egg?	*Eun-Jung Rhee (Sungkyunkwan Univ.)*
08:10-08:30	Discussion	
14:00-15:40	**The Liver Week Satellite Symposium for Regeneration Medicine**	*Shuji Terai (Niigata Univ., Japan), Soon Koo Baik (Yonsei Univ. Wonju)*
14:00-14:20	Comparison of Bone Marrow-Derived Mesenchymal Stem Cells Isolated from Normal and Cirrhotic Patients	*Young Woo Eom (Yonsei Univ. Wonju)*
14:20-14:40	Feasibility of Enhanced PRL-1 in Placenta-Derived Mesenchymal Stem Cells by Gene Modification on a Rat Model with Hepatic Failure	*Gi Jin Kim (CHA Univ.)*
14:40-15:00	Vascularized Liver Tissues with Different Types of Endothelial Cells and Recovery Aids for Acute Liver Failure	*Soo Hyun Kim (KIST)*
15:00-15:20	MicroRNA Profile Analysis in Liver Fibrotic Tissue and Hepatic Differentiated Human Bone Marrow-Derived Mesenchymal Stem Cells	*Jung Hoon Cha (The Catholic Univ. of Korea)*
15:20-15:40	Proteomics Approach for Translational Research, Focusing on Liver Disease	*Kyunggon Kim (Univ. of Ulsan)*

ROOM A [2F] 201-202

K: Session in Korean

08:30-09:30	**KLTS Symposium 1. Conundrum: Transplanted Liver Pathology**	*Shin Hwang (Univ. of Ulsan), Haeryoung Kim (Seoul National Univ.)*
08:30-09:10	Liver Allograft Pathology: Developments in Antibody-Mediated Rejection	*Christopher Bellamy (The Univ. of Edinburgh, UK)*
09:10-09:30	Is a Protocol Biopsy Needed in a Liver Recipient?	*Suk Kyun Hong (Seoul National Univ.)*
11:10-12:10	**KAHBPS-KLTS Joint Symposium. Diagnosis and Management of Combined Hepatocellular Carcinoma (HCC) and Cholangiocellular Carcinoma (CCC)**	*Hee Chul Yu (Chonbuk National Univ.), Young Kyoung You (The Catholic Univ. of Korea)*
11:10-11:25	Pathological Point of View of Combined HCC and CCA: What Is the Origin and Diagnostic Criteria of Combined HCC and CCA?	*Young Nyun Park (Yonsei Univ.)*
11:25-11:40	Imaging Features of Combined HCC and CCC: What Is the Difference Compared with HCC or CCC?	*Chang-Hee Lee (Korea Univ.)*
11:40-11:55	Surgical Treatment and Prognosis of Combined HCC and CCC	*Ryusei Matsuyama (Yokohama City Univ., Japan)*
11:55-12:10	Issues of Combined HCC and CCC in Liver Transplantation	*Young Seok Han (Kyungpook National Univ.)*
12:10-13:10	**KLTS General Meeting** / Luncheon Symposium 5 [Astellas]	
13:10-13:30	Break	
13:30-14:00	**KLTS Special Lecture**	*Kyung-Suk Suh (Seoul National Univ.)*
13:30-14:00	Donation after Circulatory Death Liver Procurement in Real Practice	*Koji Hashimoto (Cleveland Clinic, USA)*
14:10-15:30	**KLTS Symposium 2. Use of Donation after Circulatory Death to Overcome the Decrease of Brain Death Donor** (*K)	*Yang Won Nah (Univ. of Ulsan), Myoung Soo Kim (Yonsei Univ.)*
14:10-14:30	Current Status and Problems of Organ Donation in Korea	*Won-Hyun Cho (Korea Organ Donation Agency)*
14:30-14:50	Current Status of Liver Allocation System	*Jae Geun Lee (Yonsei Univ.)*
14:50-15:10	Institutional Issue and Limit of Donation after Cardiac Death	*Dong-Sik Kim (Korea Univ.)*
15:10-15:30	Panel Discussion	*Jeong Rim Lee (Korea Organ Donation Agency), Myeongyong Seo (Korea Centers for Disease Control and Prevention)*
15:30-16:30	Poster Round	**Grand Ballroom** [3F]
16:30-17:50	**KASL-KLTS Joint Symposium: Hepatorenal Syndrome (HRS)** (K*)	*Jae-Won Joh (Sungkyunkwan Univ.), Jong Young Choi (The Catholic Univ. of Korea)*
16:30-16:50	HRS: Definition, Pathophysiology, and Management	*Yeon Seok Seo (Korea Univ.)*
16:50-17:10	When to Consider Simultaneous Liver Kidney Transplantation and How to Prevent Adverse Renal Outcome after Liver Transplantation	*Jae Min Chun (Kyungpook National Univ.)*
17:10-17:30	MELD Purgatory in HRS and Allocation Policy: When to Start Renal Replacement Therapy?	*Shin Hwang (Univ. of Ulsan)*
17:30-17:50	When to Start Renal Replacement Therapy for Hepatorenal Syndrome	*Hye Ryoun Jang (Sungkyunkwan Univ.)*

ROOM B [2F] 203

14:10-15:30	**KLTS Coordinator Session** (K*)	*Kyung-Ock Jeon (Severance Hospital), Sunyoung Son (Gangnam Severance Hospital)*
14:10-14:30	Recovery Management for Old Age Recipient	*Man Ki Ju (Yonsei Univ.)*
14:30-14:50	Transplantation Counseling for an Elderly Liver Transplantation Patient	*Hyung Sook Kim (Seoul St. Mary's Hospital)*
14:50-15:10	Acute Liver Failure	*Dong Jin Joo (Yonsei Univ.)*
15:10-15:30	Patient Management after Liver Transplantation	*Seung Heui Hong (Samsung Medical Center)*

ROOM D [2F] 205

K: Session in Korean

08:30-09:30	**KLCA Symposium 1. A Developing Strategy to Improve Diagnosis of HCC**	*Jin Wook Chung (Seoul National Univ.), June Sung Lee (Inje Univ.)*
08:30-08:50	Surveillance for HCC in Patients with Non-Alcoholic Fatty Liver Disease	*Vincent Wong (The Chinese Univ. of Hong Kong, Hong Kong)*
08:50-09:10	Are Emerging Biomarkers and Imaging Tools Better than Routine Abdominal Sonography for HCC Surveillance?	*Do Young Kim (Yonsei Univ.)*
09:10-09:30	Is LI-RADS Better for Diagnosis of HCC?	*Jeong Min Lee (Seoul National Univ.)*
11:10-12:10	**KLCA General Meeting** (*K)	
11:10-11:25	0202 Liver Cancer Day Special Lecture	*Hyun Woong Lee (Yonsei Univ.)*
11:25-12:10	KLCA General Meeting	
12:10-13:10	Luncheon Symposium 6 [Bayer]	
13:10-13:30	Break	
13:30-14:30	**LCSGJ-KLCA Joint Symposium 1. One Step Forward for Understanding Basic Knowledge**	*Yutaka Kawakami (Keio Univ., Japan), Young Nyun Park (Yonsei Univ.)*
13:30-13:50	Potential of Exosome-Carrying MicroRNAs in Liquid Biopsy	*Takahiro Ochiya (Tokyo Medical Univ., Japan)*
13:50-14:10	T Cell Based Adoptive Cell Therapy for Solid Cancers	*Yutaka Kawakami (Keio Univ., Japan)*
14:10-14:30	Oncolytic Virus-Based Therapy for HCC	*Jeong Heo (Pusan National Univ.)*
14:30-15:30	**LCSGJ-KLCA Joint Symposium 2. Similarities and Differences in Treatment of HCC**	*Shoji Kubo (Osaka City Univ., Japan), Seung Kew Yoon (The Catholic Univ. of Korea)*
14:30-14:45	Recent Trends of Treatment for Intermediate Stage HCC: Japanese Experience	*Masatoshi Kudo (Kindai Univ., Japan)*
14:45-15:00	Recent Trends of Treatment for Intermediate Stage HCC: Korean Experience	*Ji Hoon Kim (Korea Univ.)*
15:00-15:15	Recent Trends of Treatment for Advanced Stage HCC: Japanese Experience	*Kazuomi Ueshima (Kindai Univ., Japan)*
15:15-15:30	Recent Trends of Treatment for Advanced Stage HCC: Korean Experience	*Won Young Tak (Kyungpook National Univ.)*
15:30-16:30	Poster Round	
16:30-17:50	**KLCA Symposium 2. New and Emerging Systemic Therapies in Advanced HCC**	*Kwang-Hyub Han (Yonsei Univ.), Seung Woon Paik (Sungkyunkwan Univ.)*
16:30-16:50	First Line Treatments for HCC	*Arndt Vogel (Hannover Medical School, Germany)*
16:50-17:10	Second Line Treatments for HCC	*Stephen L. Chan (The Chinese Univ. of Hong Kong, Hong Kong)*
17:10-17:30	A Future of Systemic Agents: Emerging Therapies and Strategies	*Baek-Yeol Ryoo (Univ. of Ulsan)*
17:30-17:50	Combination of Interventional and Systemic Therapies for HCC: Current Status and Future Direction	*Joong-Won Park (National Cancer Center)*

ROOM F [2F] 207

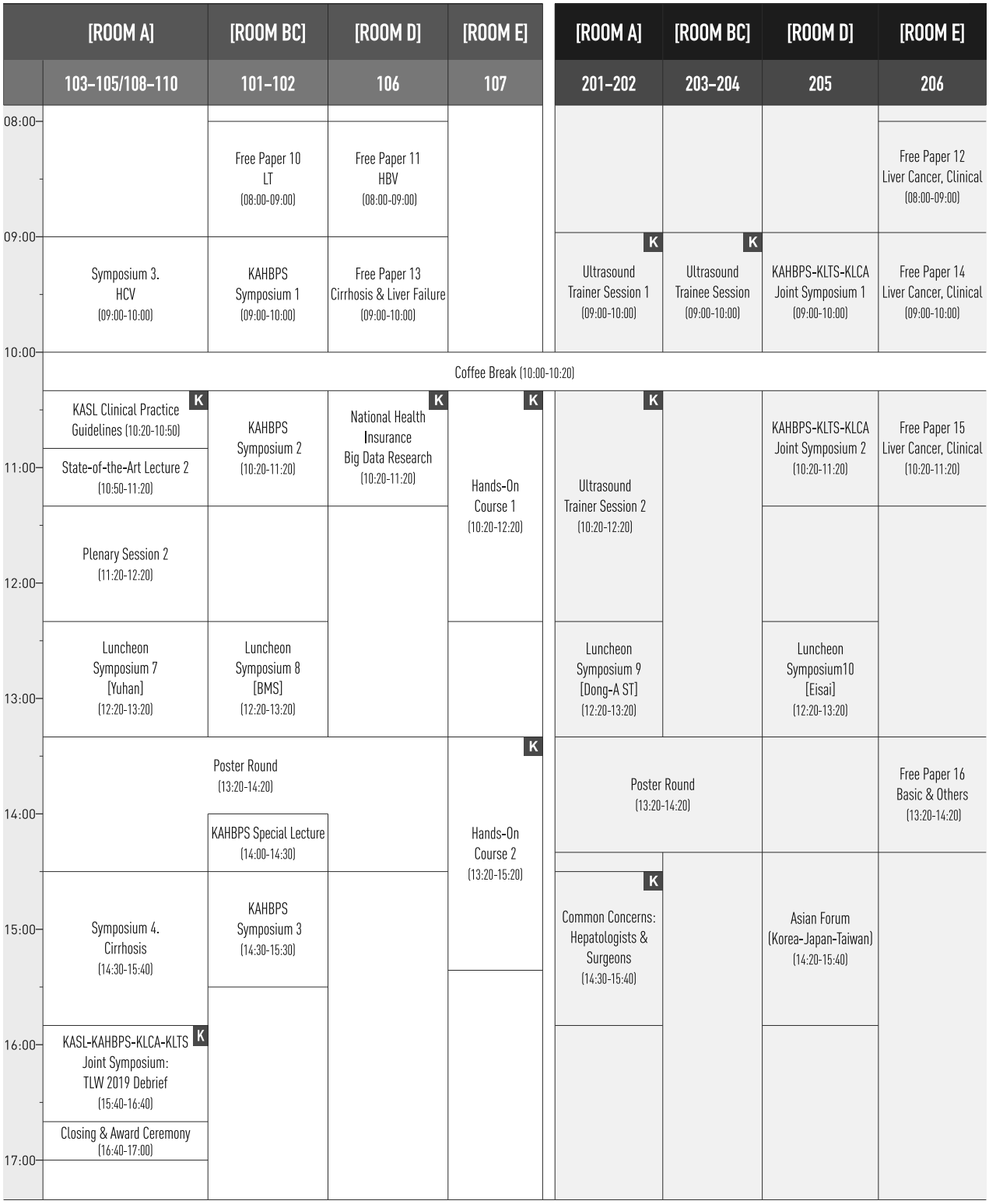
*KSJA: Korea Science Journalists Association

15:30-16:30	**KSJA-The Liver Week 2019 Press Forum. Liver Disease Control in Korea** (*K)	*Kang Mo Kim (Univ. of Ulsan)*
15:30-15:40	Current Status and Suggestion for Eradication of Chronic Hepatitis C in Korea	*Do Young Kim (Yonsei Univ.)*
15:40-15:50	Epidemic of Acute Hepatitis A in Korea: Vaccination Policy	*Ji Hoon Kim (Korea Univ.)*
15:50-16:00	Discussion	
16:00-16:10	The Liver Week 2019 Highlight Presentation	*Bo Hyun Kim (National Cancer Center)*
16:10-16:20	Unresolved Reimbursement Issues in Liver Disease	*Hyung Joon Kim (Chung-Ang Univ.)*
16:20-16:30	Discussion	

PROGRAM AT A GLANCE

DAY 3 Saturday, June 22, 2019

K: Session in Korean



The Korean Association for the Study of the Liver (KASL)
The Korean Liver Transplantation Society (KLTS)

The Korean Association of HBP Surgery (KAHBPS)
The Korean Liver Cancer Association (KLCA)

ROOM A [1F] 103-105 / 108-110

K: Session in Korean

09:00-10:00	**Symposium 3. Hepatitis C Virus**	*Masao Omata (Yamanashi Prefectural Central Hospital, Japan), Si Hyun Bae (The Catholic Univ. of Korea)*
09:00-09:20	Long-Term Outcome of Direct-Acting Antiviral Treatment	*Jung Il Lee (Yonsei Univ.)*
09:20-09:40	Follow-Up Strategies Following Cure of Hepatitis C Virus Infection	*Naoya Sakamoto (Hokkaido Univ., Japan)*
09:40-10:00	Unmet Needs in the Era of Direct-Acting Antiviral Therapy	*Ming-Lung Yu (Kaohsiung Medical Univ., Taiwan)*
10:00-10:20	Coffee Break	
10:20-10:50	**Special Session. KASL Clinical Practice Guidelines** (*K)	*Kwan Soo Byun (Korea Univ.)*
10:20-10:50	Variceal Bleeding and Hepatic Encephalopathy	*Jae Young Jang (Soonchunhyang Univ.)*
10:50-11:20	**State-of-the-Art Lecture 2**	*Jin Mo Yang (The Catholic Univ. of Korea)*
10:50-11:20	Current Understanding of Autoimmune Liver Diseases	*Atsushi Tanaka (Teikyo Univ., Japan)*
11:20-12:20	**Plenary Session 2**	*Joong-Won Park (National Cancer Center), Han Chu Lee (Univ. of Ulsan), Myung-Hee Yoon (Pusan National Univ.)*
12:20-13:20	Luncheon Symposium 7 [Yuhan]	
13:20-14:20	Poster Round	**Grand Ballroom** [3F]
14:30-15:40	**Symposium 4. Cirrhosis**	*Rino Gani (Univ. of Indonesia, Indonesia), Soon Koo Baik (Yonsei Univ. Wonju)*
14:30-14:50	Mesenchymal Stem Cell Therapy for Liver Cirrhosis (Basic Study and Clinical Application)	*Shuji Terai (Niigata Univ., Japan)*
14:50-15:10	The Role of Albumin Related with Systemic Inflammation in Cirrhosis	*Paolo Angeli (Univ. of Padova, Italy)*
15:10-15:30	Role of Cytoglobin, a Novel Radical Scavenger in Stellate Cell Activation and Hepatic Fibrosis	*Norifumi Kawada (Osaka City Univ., Japan)*
15:30-15:40	Discussion	
15:40-16:40	**KASL-KAHBPS-KLCA-KLTS Joint Symposium: The Liver Week 2019 Debrief** (*K)	*Sang Hoon Ahn (Yonsei Univ.), Dong-Sik Kim (Korea Univ.), Ji Hoon Kim (Korea Univ.)*
15:40-15:55	Best Presentations of KASL	*Jun Yong Park (Yonsei Univ.)*
15:55-16:10	Best Presentations of KAHBPS	*Say-June Kim (The Catholic Univ. of Korea), Sae Byeol Choi (Korea Univ.)*
16:10-16:25	Best Presentations of KLCA	*Su Jong Yu (Seoul National Univ.)*
16:25-16:40	Best Presentations of KLTS	*Jae Geun Lee (Yonsei Univ.)*
16:40-17:00	Closing and Award Ceremony	

ROOM BC [1F] 101-102

09:00-10:00	**KAHBPS Symposium 1. Surgical Research in HBP Field-Challenges and Barriers**	*Il-Young Park (The Catholic Univ. of Korea), Koo Jeong Kang (Keimyung Univ.)*
09:00-09:20	Surgeon-Scientists: An Endangered Species?	*Sundeep G. Keswani (Baylor College of Medicine, USA)*
09:20-09:40	Basic/Translational Research (How to Start and Grow)	*Say-June Kim (The Catholic Univ. of Korea)*
09:40-10:00	Clinical Research to Reduce Pancreatic Fistula after Distal Pancreatectomy	*Manabu Kawai (Wakayama Medical Univ., Japan)*
10:00-10:20	Coffee Break	

ROOM BC [1F] 101-102

K: Session in Korean

10:20-11:20	**KAHBPS Symposium 2. Clinical Issues in Non-Hepatic Abdominal Surgery in Patients with Liver Cirrhosis**	*Hyung Chul Kim (Soonchunhyang Univ.), Yang Won Nah (Univ. of Ulsan)*
	Management of Gallstones and Acute Cholecystitis in Patient with Liver Cirrhosis	
10:20-10:35	1) Medical Treatment: Indication and Result of Medical Treatment	*Ki Tae Suk (Hallym Univ.)*
10:35-10:50	2) Surgical Treatment: What Should We Caution to Consider Surgery?	*Shang Yu Wang (Chang-Gung Univ., Taiwan)*
10:50-11:05	Clinical Outcomes and Prognosis of Emergency Surgery in Liver Cirrhosis Patient	*Fausto Catena (Univ. of Bologna, Italy)*
11:05-11:20	Elective Cancer Surgery in Patients with Liver Cirrhosis	*Sae Byeol Choi (Korea Univ.)*
12:20-13:20	Luncheon Symposium 8 [BMS]	
13:20-14:20	Poster Round	**Grand Ballroom** [3F]
14:00-14:30	**KAHBPS Special Lecture**	*Hee Chul Yu (Chonbuk National Univ.)*
14:00-14:30	The Journey from Scientific Idea to Funded Grant: A Surgeon's Approach	*Sundeep G. Keswani (Baylor College of Medicine, USA)*
14:30-15:30	**KAHBPS Symposium 3. Focus Review of Advanced Gallbladder Cancer Treatment**	*Dong Wook Choi (Sungkyunkwan Univ.), Sang-Jae Park (National Cancer Center)*
14:30-14:50	The Operative Indication of Advanced Gallbladder Cancer: How Much Advance Is the Limitation?	*Masayuki Ohtsuka (Chiba Univ., Japan)*
14:50-15:10	Recent Advances in the Chemotherapy in Advanced Gallbladder Cancer: Palliative vs. Neoadjuvant Chemotherapy	*Hei-Cheul Jeung (Yonsei Univ.)*
15:10-15:30	Case Presentation	*Chi-Young Jeong (Gyeongsang National Univ.)*

ROOM D [1F] 106

10:20-11:20	**Special Session. National Health Insurance Big Data Research** (*K)	*Hyoung-Soo Kang (National Health Insurance Service), Jaeyoun Cheong (Ajou Univ.)*
10:20-10:35	National Health Insurance Big Data Analysis: Process and Example	*Seong Yong Park (National Health Insurance Service)*
10:35-10:50	National Health Insurance Big Data Research: HCC Surveillance	*Yong-Han Paik (Sungkyunkwan Univ.)*
10:50-11:05	Role of Statins on Development and Progression of Non-Alcoholic Fatty Liver Disease: A Nationwide Nested Case-Control Study	*Jung Il Lee (Yonsei Univ.)*
11:05-11:20	National Health Insurance Big Data Research: Liver Cirrhosis	*Dae Won Jun (Hanyang Univ.)*

ROOM A [2F] 201-202

12:20-13:20	Luncheon Symposium 9 [Dong-A ST]	
13:20-14:20	Poster Round	**Grand Ballroom** [3F]
14:30-15:40	**Common Concerns: Hapatologists and Surgeons** (*K)	*Yung Sang Lee (Univ. of Ulsan), Sung Su Yun (Yeungnam Univ.)*
14:30-14:45	Assessment of Surgical Risk in Patients with Cirrhosis	*Ki Tae Yoon (Pusan National Univ.)*
14:45-15:00	Determination of Preoperative Liver Function and Extent of Resection	*Bong-Wan Kim (Ajou Univ.)*
15:00-15:15	Prophylaxis of Hepatitis B Virus Reactivation after Liver Transplantation	*Jae Hyun Han (The Catholic Univ. of Korea)*
15:15-15:30	Optimal Hepatitis C Virus Treatment Strategy for Patients Waiting for Liver Transplantation	*In Hee Kim (Chonbuk National Univ.)*
15:30-15:40	Discussion	

ROOM D [2F] 205

K: Session in Korean

09:00-10:00	**KAHBPS-KLTS-KLCA Joint Symposium 1. Unresolved Issues in HCC: Medical and Interventional Radiology**	*Yun Hwan Kim (Korea Univ.), Jaeseok Hwang (Keimyung Univ.)*
09:00-09:20	Adjuvant Therapy after Curative Treatment: Enough or Still Lacking?	*Su Jong Yu (Seoul National Univ.)*
09:20-09:40	Direct Acting Antiviral and HCC in Chronic Hepatitis C: Friend or Foe?	*Hyung Joon Kim (Chung-Ang Univ.)*
09:40-10:00	How to Overcome Long-Term Decline in Survival of HCC Patients Treated with Ablation	*Shuichiro Shiina (Juntendo Univ., Japan)*
10:00-10:20	Coffee Break	
10:20-11:20	**KAHBPS-KLTS-KLCA Joint Symposium 2. Unresolved Issues in HCC: Surgical and Radiation Oncology**	*Hee Jung Wang (Ajou Univ.), Jinsil Seong (Yonsei Univ.)*
10:20-10:40	Will Laparoscopic Approach Be Almighty Weapon in Surgery in HCC	*Jong Man Kim (Sungkyunkwan Univ.)*
10:40-11:00	Priority Policy for Patients with HCC Awaiting Liver Transplantation: Unresolved Issue?	*Dorry L. Segev (Johns Hopkins Univ., USA)*
11:00-11:20	Radiation Therapy for Early HCC: Will It Be a Good Option in Practice?	*Sang Min Yoon (Univ. of Ulsan)*
12:20-13:20	Luncheon Symposium 10 [Eisai]	
13:20-14:20	Poster Round	**Grand Ballroom** [3F]
14:20-15:40	**Asian Forum: Korea-Japan-Taiwan**	*Jin Mo Yang (Korea), Tetsuo Takehara (Japan), Jia-Horng Kao (Taiwan)*
14:20-14:35	Current Status and Emerging Issues in Liver Diseases in Japan	*Hayato Hikita (Osaka Univ., Japan)*
14:35-14:50	Current Status and Emerging Issues in Liver Diseases in Taiwan	*Chun-Jen Liu (National Taiwan Univ., Taiwan)*
14:50-15:05	Current Status and Emerging Issues in Liver Diseases in Korea	*Yoon Jun Kim (Seoul National Univ.)*
15:05-15:25	Cirrhotic Portal Hypertension: From Arterial Vasodilatation to Systemic Inflammation	*Han-Chieh Lin (National Yang-Ming Univ., Taiwan)*
15:25-15:40	Discussion	

ULTRASONOGRAPHY (USG) TRAINING COURSE & HANDS-ON COURSE

K: Session in Korean

ROOM A [2F] 201-202

09:00-10:00	**USG Session 1. Upgrading the USG Education** (*K)	*Soon Koo Baik (Yonsei Univ. Wonju)*
09:00-09:15	Current Status of USG Education Program and USG Specialist Certificates of KASL	*Hyung Joon Yim (Korea Univ.)*
09:15-09:35	How Do I Teach Abdominal USG for Trainee?	*Yun Soo Kim (Gachon Univ.)*
09:35-10:00	How to Perform Contrast-Enhanced USG: Experiences in Japan	*Fuminori Moriyasu (Int'l Univ. of Health and Welfare, Japan)*
10:00-10:20	Coffee Break	
10:20-12:20	**USG Session 2. Diversifying the Field of USG for Training** (*K)	*Won Young Tak (Kyungpook National Univ.)*
10:20-10:40	Setting-Up an Abdominal USG Facility and Training Program	*In Hee Kim (Chonbuk National Univ.)*
10:40-11:00	Tips for Selection and Maintenance of USG Machines	*Hyun Joo Kim (GE), Han Jong Yu (Canon)*
11:00-11:20	Assessment of Hepatic Fibrosis with 2-Dimensional Real-Time Shear Wave Elastography	*Joo Hyun Sohn (Hanyang Univ.)*
11:20-11:40	How to Improve Precision in Targeting Focal Lesion	*Shuichiro Shiina (Juntendo Univ., Japan)*
11:40-12:00	New Insight for Lower Abdomen and Kidney USG	*Seong Sook Hong (Soonchunhyang Univ.)*
12:00-12:20	Present and Future of National Health Insurance System for USG: What Do We Need to Prepare for?	*Hong Soo Kim (Soonchunhyang Univ.)*

ROOM BC [2F] 203-204

09:00-10:00	**USG Trainee Session** (*K)	*Young Seok Kim (Soonchunhyang Univ.)*
09:00-09:20	How to Utilize the Various Functions of USG Machine	*Moon Young Kim (Yonsei Univ. Wonju)*
09:20-09:40	Basic Liver Scanning and Key Findings	*Jeong Eun Song (Daegu Catholic Univ.)*
09:40-10:00	Pancreatobiliary USG Scanning Made Easy	*Soon Sun Kim (Ajou Univ.)*

ROOM E [1F] 107

10:20-12:20	**Hands-on Course I** (*K)
Tutors	*Sae Hwan Lee (Soonchunhyang Univ.), Won Sohn (Sungkyunkwan Univ.), Do Seon Song (The Catholic Univ. of Korea), Chung Hwan Jun (Chonnam National Univ.), Sung Won Lee (The Catholic Univ. of Korea), Sun Hong Yoo (The Catholic Univ. of Korea)*
13:20-15:20	**Hands-on Course II** (*K)
Tutors	*Jae Young Jang (Soonchunhyang Univ.), Jaeyoun Cheong (Ajou Univ.), Yeon Seok Seo (Korea Univ.), Sang Gyune Kim (Soonchunhyang Univ.), Moon Young Kim (Yonsei Univ. Wonju), Ki Tae Suk (Hallym Univ.)*

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Special Lectures with Debates: Can We Discontinue Hepatitis B Virus Therapy? *Pros. vs. Cons.*

State-of-the-Art Lecture 1

Symposium 2. Hepatitis B Virus

Clinical Hepatology Update. Clinical Trials of Management in Chronic Liver Diseases (*K)

Hepatology Associates Course (*K)

The Liver Week Satellite Symposium for Regeneration Medicine

KLTS Symposium 1. Conundrum: Transplanted Liver Pathology

KAHBPS-KLTS Joint Symposium. Diagnosis and Management of Combined Hepatocellular Carcinoma (HCC) and Cholangiocellular Carcinoma (CCC)

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State-of-the-Art Lecture 2

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KAHBPS Symposium 2. Clinical Issues in Non-Hepatic Abdominal Surgery in Patients with Liver Cirrhosis

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KAHBPS Symposium 3. Focus Review of Advanced Gallbladder Cancer Treatment (*K)

Special Session. National Health Insurance Big Data Research (*K)

Common Concerns: Hapatologists and Surgeons (*K)

KAHBPS-KLTS-KLCA Joint Symposium 1. Unresolved Issues in HCC: Medical and Interventional Radiology

KAHBPS-KLTS-KLCA Joint Symposium 2. Unresolved Issues in HCC: Surgical and Radiation Oncology

Asian Forum: Korea-Japan-Taiwan

USG Session 1. Upgrading the USG Education (*K)

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USG Session 2. Diversifying the Field of USG for Training (*K)

USG Trainee Session (*K)

Plenary Session 1

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Free Paper Session

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2. ALD & NAFLD

3. Liver Cancer, Basic

4. Cirrhosis & Liver Failure

5. HCV

6. Liver Cancer

7. Surgery, Biliary

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9. ALD & NAFLD

10. Liver Transplantation

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12. Liver Cancer, Clinical

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Oral Poster Presentation

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Contents

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Liver Cirrhosis, Portal Hypertension with Cx., Clinical

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Contents

DAY 1: Thursday, June 20, 2019 (10:50-12:30)
ROOM D [2F] 205

Basic Forum 1

Hepatitis Virus (*K)

Chairs:
Soon Bong Hwang (Chonbuk National Univ.)
Jin-Wook Kim (Seoul National Univ.)

Molecular Basis for Cure of Hepatitis B Virus Infection

Kyun-Hwan Kim

Department of Pharmacology, Konkuk University School of Medicine, Seoul, Korea

More than 240 million people are chronically infected with hepatitis B virus (HBV), with some 600,000 deaths per year attributed to the virus. Chronic HBV infection is associated with significant morbidity and mortality, fibrosis, cirrhosis, end-stage liver diseases and primary hepatocellular carcinoma (HCC). However, the current antiviral drugs can efficiently control but not eliminate HBV in the carriers at risk to develop liver diseases and cancer. HBV patients often require lifelong therapies and cure is still a challenging goal because HBV establishes a stable nuclear persistence form, the so-called HBV cccDNA, in infected hepatocytes. Eliminating HBV cccDNA is a critical issue if we want to cure HBV infection.

To achieve functional or complete cure of HBV, ICE-HBV (The International Coalition to Eliminate HBV) forum was created in 2016. ICE-HBV tries to accelerate HBV cure research by proposing two strategies, namely curing of HBV infection without killing infected cells and inducing immune control to safely eliminate infected cells. These approaches will be introduced in this presentation.

Recent advances in basic HBV sciences have heralded a new horizon of innovative therapeutic approaches to the possibility of a functional cure of chronic HBV infection. These approaches include inhibitors of viral entry, cccDNA modulators, interfering RNA targeting viral RNAs, novel polymerase or ribonuclease H inhibitors, core protein allosteric modulators and capsid assembly modulators (capsid inhibitors), drugs interfering with HBx function, drugs targeting viral and HBsAg egress, or agents restoring the host immunity against HBV.

In this talk, I review the current state of science in HBV therapy and highlight new therapeutic strategies spurred by recent scientific advances in HBV field. Especially, I will focus on the action mechanisms of those approaches in detail and introduce the limitations of current strategies.

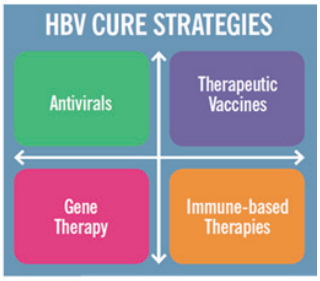
Keywords: Hepatitis B virus (HBV), Covalently closed circular DNA (cccDNA), HBV cure, Capsid inhibitor, HBsAg inhibitor

International Coalition to Eliminate the Hepatitis B Virus (ICE-HBV)

ICE-HBV

Associated working groups
- Academia (basic and clinical sciences)
- Industry
- Drug agencies (FDA, EMA)
- International scientific societies (AASLD, ALEH, APASL, EASL, others)
- Funding research agencies (ANRS, DZIF, others)
- Nonprofit organizations (Hepatitis B foundation, others)
- WHO
- HBV-affected community

Virology | **Immunology** | **Innovative tools** | **Clinical trials**



1. Curing of HBV infection without killing infected cells
2. Inducing immune control to safely eliminate infected cells

Overview of Current HBV Drug Development

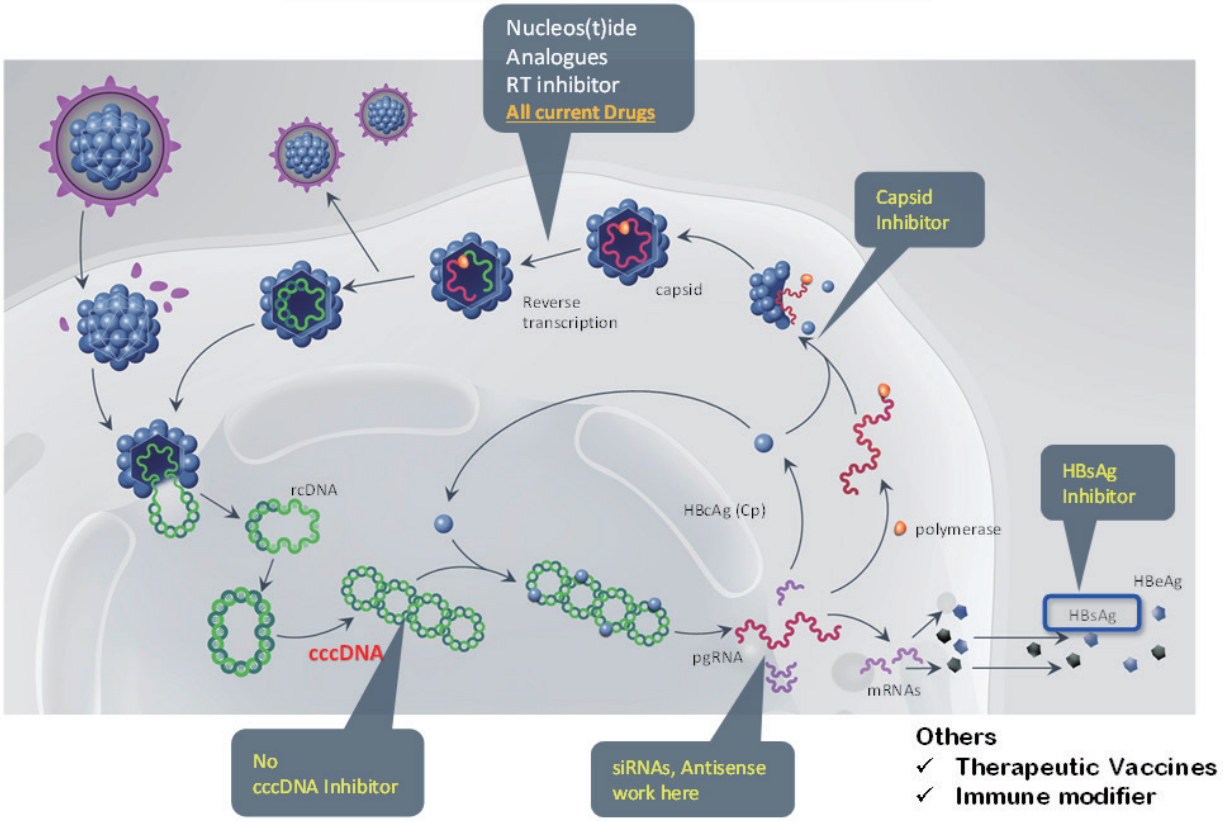


Table. Capsid Inhibitors in Development (updated May 2019)

Capsid Inhibitors: Interferes with the viral DNA protein shield				
Morphothiadin (GLS4)	Capsid inhibitor	HEC Pharma, PR China	pharm.hec.cn/en	Phase II
JNJ 56136379	Capsid inhibitor	Janssen, Scotland	janssen.com	Phase II
ABI-H0731	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Phase II
AB-423	Capsid inhibitor	Arbutus Biopharma, USA	arbutusbio.com	Phase I
AB-506	Capsid inhibitor	Arbutus Biopharma, USA	arbutusbio.com/	Phase I
ABI-H2158	Capsid inhibitor	Assembly Biosciences, USA	assemblybio.com	Phase I
RG7907	Capsid inhibitor	Roche, Switzerland	roche.com	Phase I
QL-007	Capsid inhibitor	Qilu, China	qilu-pharma.com	Phase I
GLP-26	Capsid inhibitor	Emory University	emory.edu	Preclinical
EP-027367	Capsid inhibitor	Enanta Pharmaceuticals, USA	enanta.com	Preclinical
QL-0A6a	Capsid inhibitor	Qilu, China	qilu-pharma.com	Preclinical
CB-HBV-001	Capsid inhibitor	ZhiMeng Biopharma, China	core-biopharma.com	Preclinical

Drug Development for Hepatitis B Virus Treatment

Sung-Gyoo Park

School of Life Sciences, Gwangju Institute of Science and Technology, Gwangju, Korea

Hepatitis B virus (HBV) is a double-stranded DNA virus and Hepadnaviridae virus.[4,7] Chronic HBV infection is a major global cause of hepatocellular carcinoma (HCC). Chronic carriers increase liver cancer risk by over 100 times. HBV can be treated with nucleosides (nAs) that inhibit HBV polymerases such as tenofovir (TDF) and entecavir (ETV). Both are potent and have a high genetic barrier to drug resistance. However, HBV can not be cured due to the excellent stability of viral cccDNA intermediates that are not directly targeted by NA.[1] Combination therapy with NA and peginterferon α2a (pegIFNα2a) can improve treatment effectiveness. These combination therapies can cause synergy because they induce antiviral and immunomodulatory activities. In fact, the combination of TDF and pegIFNα2a results in a better hepatitis B surface antigen (HBsAg) loss than monotherapy. However, the combined ratio is still only 9.1%.[5] Also, many patients can not tolerate pegIFNα2a.[6] Therefore, new treatments are needed for patients with chronic HBV infection. In particular, a cure that directly exterminates cccDNA in the liver and continuously treats HBV infection. This goal has recently been greatly enhanced by significant advances in understanding the HBV life cycle, including how the virus enters the host cell,[3] how the cccDNA is formed,[2] how the HBV capsid is assembled,[8] and so on. Insights into these mechanisms have led to the development of many new drugs for investigating HBV, including current research.

B 형 간염 바이러스 (HBV)는 이중 가닥 DNA 바이러스이며 Hepadnaviridae 계열의 바이러스이다.[4,7] 만성 HBV 감염은 간세포 암 (HCC)의 주요 원인이다. 만성 보균자는 간암 발생 위험이 100 배 이상 증가한다. HBV는 테 노포 비르 (TDF) 및 엔테카비어 (ETV)와 같은 HBV 중합효소를 억제하는 뉴 클레오 시드 (NAs)가 치료제로 쓰이고 있다. 둘 다 유력하고 약물 내성에 대한 유전 적 장벽이 높으나, cccDNA의 현저한 안정성 때문에 HBV를 완벽히 치료할 수 없으며, 또한, NAs에 의해 조절받지 않는다.[1] 치료 효과는 add-on 또는 switch regimens에서 NA를 peginterferon α2a (pegIFNα2a)와 병용하면 개선 될 수 있다. 이 병용 요법은 항 바이러스 및 면역 조절 활성을 유도하기 때문에 시너지로 작용한다. 실제로, TDF와 pegIFNα2a 조합은 단독 요법보다 B 형 간염 표면 항원 (HBsAg) 손실을 더 잘 유도한다. 그러나 치료 효율은 여전히 9.1 %에 불과하다.[5] 또한 많은 환자가 pegIFNα2a를 견딜 수 없다.[6] 따라서 만성 HBV 감염 환자에게는 새로운 치료법이 필요하다. 특히, 간내 cccDNA를 직접 근절하고 지속적으로 HBV 감염을 치료하는 치료법이 필요하다. 여기서는 바이러스가 숙주 세포에 어떻게 들어가는가,[3] cccDNA가 어떻게 형성되는지,[2] HBV 캡시드가 어떻게 조립되는지[8] 등을 포함하여 HBV 수명주기를 이해가 이 바이러스에 대한 치료제 개발에 크게 기여하고 있다. 이러한 기전에 대한 연구는 현재의 HBV에 대한 많은 새로운 약제 개발로 이어지고 있다.

References

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Identification and Validation of Druggable Targets in the Hepatitis C Virus Life Cycle

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황 순 봉

전북대학교 인수공통전염병연구소 RNA바이러스질병연구실

Hepatitis C virus (HCV) is highly dependent on cellular machineries in all steps of viral life cycle for its own propagation. Blocking any step of the virus life cycle results in an efficient blockade of viral production and thus could be a potential target for viral therapy. To develop drugs with broad-spectrum antiviral activities using host factors as putative druggable targets, we employed various high-throughput screening strategies, including mass spectrometry-based immunoprecipitation proteomics, tandem affinity purification, siRNA library screening, protein microarray screening, and transcriptome sequencing methods. Using these technologies, we have identified highly promising candidates of HTAs against HCV. Among these, tylophorine, the natural plant product, efficiently abrogated HCV replication. Moreover, tylophorine intermediates, 5-Oxo-1-[(2,3,6,7-tetramethoxy-9-phenanthrenyl) methyl]-L-proline (O859585) displayed an anti-HCV activity at the attachment step of the HCV life cycle by neutralizing free viral particles. Of note, co-treatment of O859585 with either interferon alpha (IFNα) or sofosbuvir exerted an additive antiviral activity in HCV-infected cells. Most importantly, O859585 in combination with IFNα and sofosbuvir exhibited synergistic effects on anti-HCV activity in primary human hepatocytes. These data suggest that O859585 may be a novel antiviral agent for HCV therapy. We hope that these newly identified host-targeted antivirals (HTAs) might be novel and potent therapeutic agents for patients who have failed prior direct-acting antiviral-based therapy. Moreover, we can apply these HTAs as therapeutic candidates for combination therapy.

Keywords: HCV, High-throughput screening, Druggable targets, Direct-acting antivirals, Host-targeted antivirals

Hepatitis C Virus Vaccine Development

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Prophylactic hepatitis C virus (HCV) vaccine candidates have been developed to elicit HCV-specific memory T cells and/or broadly neutralizing antibodies. In principle, only neutralizing antibodies can protect hosts from infection itself. However, virus-specific memory T cells can prevent the evolution of the infection to chronic persistent infection.

Evidence that emphasizes the crucial role of T cell responses in protective immunity to HCV infection and reinfection has accumulated from studies in patients and chimpanzees. In particular, HCV-specific memory T cells protect HCV-rechallenged chimpanzees and naturally reinfected patients, as shown by lower levels of the virus and a shorter duration of viraemia, which supports the rationale of developing T cell-based vaccines.

The key immunological factors for successful vaccine-induced protective immunity are the early proliferation of polyfunctional $CD8^+$ T cells upon HCV infection and the high levels of expression of the memory precursor marker CD127. In a recent Phase I trial in healthy human volunteers, a simian adenoviral vector expressing HCV nonstructural proteins primed HCV-specific $CD4^+$ and $CD8^+$ T cells, and a boost immunization with MVA expressing the same HCV proteins elicited sustained memory and effector T cell responses with enhanced functionality and proliferative capacity. This vaccine is currently proceeding to a Phase II trial.

In this lecture, strategies to develop prophylactic HCV vaccines will be discussed.

DAY 1: Thursday, June 20, 2019 (13:50-15:30)
ROOM D [2F] 205

Basic Forum 2

Hepatocellular Carcinoma and Steatohepatitis (*K)

Chairs:

Sang Hoon Park (Hallym Univ.)
Yong-Han Paik (Sungkyunkwan Univ.)

Understanding of Immune Checkpoint Inhibitors in Hepatocellular Carcinoma

Su-Hyung Park

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Immuno-oncology drugs are considered as a breakthrough in cancer treatment because of their ability to target and enable immune cells to destroy cancer cells. The immune system is the body's natural defense system, attacking dangerous cells and destroy them. Cancer cells have developed the ability to 'hide' from the immune system and thereby prevent an immune response. Immunotherapies aim to enable the immune system to fight cancer. Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and several agents targeting programmed cell death-1 (PD-1), PD-L1, and cytotoxic T lymphocyte-associated protein-4 (CTLA-4) have been approved for many types of cancer. However, the therapeutic efficacy of ICIs substantially varies among cancer types and patients, and only a limited proportion of cancer patients benefit clinically from ICIs. To improve the therapeutic efficacy of cancer treatments involving ICI, the mechanisms of response to ICIs and the heterogeneous pattern of immune checkpoint receptor expression need to be better understood. Therefore, this talk will introduce the current knowledge of immunity in tumor microenvironment and the prominent recent advances for improving treatment responses of anti-PD-1 therapy in hepatocellular carcinoma (HCC). In addition, heterogeneity of tumor-specific exhausted CD8 T cells in HCC patients and its clinical implications will be discussed.

Keywords: T cell exhaustion, Hepatocellular carcinoma, Immune checkpoint receptor, PD-1, Tumor-infiltrating CD8 T cells

Hepatocarcinogenesis and Animal Model

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간암의 발생과정과 동물 모델

노 원 상

연세대학교 소화기병연구소

Hepatocellular carcinoma (HCC) is one of the most lethal cancers, causing 500,000 – 600,000 deaths worldwide each year. Hepatitis virus infection, alcohol abuse, obesity, or other factors that cause chronic liver injuries lead to hepatic fibrosis and cirrhosis. Cirrhotic liver creates a pathological microenvironment in which cells with a genetic or epigenetic alteration in cancer-related genes can become malignant. Various animal models have been developed for HCC that include chemically-induced models, xenograft models, and genetically engineered mouse models. Recently, a novel approach for genetically engineered HCC models has been developed using hydrodynamics-based transfection (HT). The HT method, which is coupled with Sleeping Beauty transposon system, has allowed a variety of HCC models expressing diverse oncogenes to be developed rapidly and cost-effectively. The versatility of HT models is expected to broaden our knowledge on the genetic mechanism underlying hepatocarcinogenesis in human.

간세포암(이후 간암)은 사망률이 높은 대표적인 암이다. 전 세계적으로 50-60만 명이 매년 간암으로 사망하고 있으며, 국내 남성에 있어서 간암은 전체 암 가운데 두 번째로 높은 사망률을 보여주고 있다. 지속적인 간 손상은 염증과 함께 간에 섬유화를 유발하며, 간섬유화가 더욱 진행되면 간경화에 이르게 된다. 이러한 손상된 간 조직 환경에서 종양유전자의 활성이나 종양억제유전자의 비활성 등이 발생하면 간암이 일어난다고 알려져 있다.

간암의 효과적인 연구를 위해서는 인간의 간암을 그대로 모방할 수 있는 동물모델이 필요하다. 간암 동물모델은 간암 발생의 유전학적인 메카니즘을 규명하고 간암 진행의 단계적 변화를 연구하는데 적극 활용될 수 있으며, 항암치료제의 효능을 예측하는 전임상 모델로서 많이 이용된다. 간암동물모델에는 간 독성물질 또는 발암 물질을 주입한 후 간암이 자연적으로 발생하도록 하는 화학적 유도 간암모델, 면역 결핍 마우스에 인간의 간암세포를 주입하여 암을 일으키는 간암 이식모델, 그리고 간암 발생과 관련된 종양유전자 및 종양억제 유전자를 조작하여 간암을 발생시키는 유전자조작 간암 모델 등이 있다. 간암 이식모델의 경우 항암 후보물질에 대해 인간의 간암세포가 어떻게 반응하는지 생체상에서 확인할 수 있어 현재 전임상 항암효능 테스트 모델로 많이 이용되고 있다. 그러나 이질적인 조직 미세환경에서 간암이 성장하므로 인간의 간암 특성과 비교해 얼마나 유사성을 가질지에 대해 많은 의구심이 든다. 또한 면역기능이 저하된 마우스에서 간암이 성장하므로 면역기반 항암치료의 효과를 연구하기에 제한이 있다. 이에 비해 유전자조작 간암모델은 인간의 간암에서 나타나는 다양한 병리학적 특성을 모방하는 간암을 발생시키며 특히, 인간의 간암에서처럼 간섬유화, 간경화를 동반하는 간암모델도 제작할 수 있다. 하지만 유전자조작 마우스를 제작하는데 오랜 기간이 걸리고 많이 비용이 드는 점은 이 모델의 큰 한계이다.

2000년대 후반부터 간암 유전자조작 마우스모델의 새로운 제작기법으로 각광을 받게 된 hydrodynamic

transfection 기법은 원하는 유전자를 발현하는 플라스미드를 혈관을 통해 간세포안으로 직접 전달하는 방법으로서, 트랜스포존 시스템을 함께 사용해 넣어준 유전자를 간세포의 genome 에 삽입시켜 지속적인 유전자 발현을 도모할 수 있다.[1] 이 방법을 사용할 경우 다양한 종양 관련 유전자 발현을 손쉽게 조작할 수 있어 현재 전 세계 많은 연구자들이 간암의 유전적 기전 연구에 적극적으로 사용하고 있다. 본 연구자의 연구그룹에서도 hydrodynamic transfection 기법을 이용해 다양한 유전자의 발현을 조작해 간세포선종 (hepatic adenoma), 분화도가 높은 간세포암부터 분화도가 낮은 간세포암, 담관암과 혼합된 간세포암 등 인간의 간암에서 나타나는 다양한 조직병리학적 특성을 띠는 간암을 발생시킬 수 있었다.[2] 또한 hydrodynamic transfection 모델 기법을 통해 다양한 종양 관련 신호경로를 유전적으로 저해하여 간암 발생을 저해할 수도 있었다. 예를 들어, hydrodynamic transfection 모델 기법으로 간경화와 간암발생에 중요한 역할을 하는 TGF-beta 신호경로를 차단할 경우 간암 발생이 현격히 줄어듦을 확인할 수 있었다.[3]

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Hepatic mGluR5 Signaling in Endocannabinoid-Mediated Alcoholic Steatosis

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엔도카나비노이드 매개 알코올성 지방간에서 mGluR5 역할

정 원 일

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간성상세포(HSCs) 유래 2-arachidonoylglycerol (2-AG)에 의한 간세포 카나비노이드 수용체 (CB1R)의 활성화는 알코올성 지방간을 유도한다. 그러나 현재까지 어떻게 알코올이 간성상세포에서 2-AG 생산을 촉진하는지 그 기전이 불분명하다. 본 연구팀에서는 만성 알코올 섭취후 생쥐와 환자 모두에서 혈장 글루타메이트 수치가 유의하게 증가됨을 관찰하였습니다. RNA-Seq분석은 에탄올 급여 마우스에서 항산화 전사인자 Nrf2를 통한 간내 시스틴-글루타메이트 교환을 유도하는 xCT의 발현이 증가됨을 보였으며, 이는 만성 알코올 섭취가 간내 시스테인 결핍 및 글루타티온 결핍을 유도해 간내 xCT의 발현을 증가시켜 시스틴을 간세포내로 이동시키는 대신 글루타메이트 배출을 초래했다. 이때 간성상세포의 글루타메이트 수용체 mGluR5의 선택적 활성이 2-AG 생성을 자극 하였다. mGluR5 또는 xCT의 유전자 결손 또는 약리학적 억제는 2-AG 생성 및 지방간 발생을 약화시켰다. 결국 알코올 섭취시 간세포의 xCT의 발현증가가 글루타메이트의 배설로 이어져 간성상세포의 mGluR5 매개 2-AG 생산을 유발한다는 결론을 얻었다. 이들을 알코올성 간손상을 예방하거나 치료할 수 있는 타겟으로 제시하고자 한다.

A key mechanism underlying alcoholic fatty liver is an endocannabinoid-induced, CB_1R-mediated increase in *de novo* lipogenesis in hepatocytes. We have earlier demonstrated that chronic alcohol treatment upregulates the hepatic levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) and its biosynthetic enzyme DAGLß in hepatic stellate cells (HSCs), and the released 2-AG acts on neighboring hepatocytes to induce CB_1R-mediated *de novo* lipogenesis, but the metabolic trigger to induce 2-AG production in HSCs remained unknown.

Here, we provide multiple lines of evidence for a bidirectional paracrine loop between hepatocytes and HSCs, where alcohol-induced oxidative stress and the resulting cysteine deficiency and glutathione (GSH) depletion triggers a compensatory upregulation of the cysteine/glutamate antiporter xCT in hepatocytes, resulting in increased glutamate secretion. Glutamate then activates the metabotropic glutamate receptor mGluR5 on neighboring HSCs to induce DAGLß expression and 2-AG production, and the released 2-AG activates CB_1R on hepatocytes to induce *de novo* lipogenesis. This bidirectional hepatocyte-HSC-hepatocytes loop represents a unique mechanism of alcoholic fatty liver and it also provides novel molecular targets for its pharmacotherapy. Indeed, we demonstrate that pharmacological blockade or genetic deletion of xCT or mGluR5 mitigates alcoholic steatosis, whereas exposure of HSCs to mGluR5 agonists promotes DAGLß expression and 2-AG production. Importantly, the key components of this bidirectional loop are similarly induced in patients with ALD. Patients with AFL have elevated circulating glutamate levels, increased expression of hepatic xCT and mGluR5, and positive correlation between mGluR5 and CB_1R-mediated lipogenesis. This reinforces the translational potential of the novel therapeutic targets identified here.

In addition, as previously reported by us and others, we adopted *in vivo* mouse models of alcoholic liver disease (ALD), *in vitro* paradigms in isolated liver cells and *in situ* hepatic perfusion techniques to clarify the role of xCT and glutamate in mitigating alcoholic oxidative stress in hepatocytes and in dissecting the mechanism of mGluR5-mediated production of 2-AG in HSCs. Chronic consumption of 40 g or more of pure alcohol per day increases the risk of end-stage liver disease and the associated social burden. Alcohol-induced ROS generation is primarily mediated via the induction of cytochrome P450 2E1 (CYP2E1), which also modulates the expression of a large repertoire of genes linked to anti-oxidative response and lipid metabolism in the context of alcoholic fatty liver. Ethanol-fed mice and ALD patients have reduced hepatic GSH levels along with hyper-homocysteinemia. This leads to abnormal hepatic accumulation and elevated serum levels of homocysteine associated with decreased concentrations of cysteine and GSH, suggesting disturbed methionine cycle and transsulfuration pathway in the liver. Our findings point to a compensatory mechanism triggered by the depletion of GSH and cysteine which involves an ethanol-induced robust induction of *Slc7a11* (encoding xCT) and *Nfe2l2* (encoding Nrf2) in hepatocytes. Interestingly, xCT and CYP2E1 are co-localized in perivenous hepatocytes in both mice and humans, suggesting a strong relationship between CYP2E1-mediated oxidative stress and xCT induction. In this context, glutamate excretion may occur predominantly around central veins, providing a plausible explanation for the preferential accumulation of fat at the perivenous zone of hepatic lobules.

In conclusion, alcohol-induced upregulation of xCT results in increased excretion of hepatic glutamate, which triggers mGluR5-mediated 2-AG production in HSCs, a pathway that could be targeted for the treatment of alcoholic fatty liver disease.

Pathogenesis of Non-Alcoholic Steatohepatitis

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비알콜성 지방간염의 병인 (G12/G13 조절계의 역할)

김상건, 김태현, 양윤미, 구자현

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Heterotrimeric G proteins converge with activated GPCRs to modulate cell-signaling pathways. Here, we report that muscle-specific ablation of Gα13 in mice promotes reprogramming of myofibers to the oxidative type, with resultant increases in systemic mitochondrial activity. Mechanistically, Gα13 and its effector RhoA suppressed NFATc1, a key regulator of myofiber conversion, by increasing Rock2-mediated phosphorylation at Ser243. Ser243 phosphorylation of NFATc1 was reduced after exercise, but was higher in obese animals. Consequently, Gα13 ablation in muscles enhanced whole-body energy metabolism, thus affording protection from diet-induced obesity and hepatic steatosis. In the absence of Gα13, Gα12 plays a role in mitochondrial regulation. Mechanistically, Gα12 stabilized SIRT1 protein through induction of USP22 via HIF-1α. Consistently, Gna12-KO mice fed a high-fat diet displayed greater susceptibility to diet-induced liver steatosis and obesity due to decrease in energy expenditure. Thus, Gα12 regulates SIRT1-dependent mitochondrial respiration through HIF-1α-dependent USP22 induction, which systemically contributes to the regulation of mitochondrial energy expenditure.

지방간과 지방간염의 진행은 에너지 이용의 저하 및 전신 대사 교란과 밀접히 관계된다. 여러 대사장기 중 골격근은 특히 에너지원을 가장 많이 소비하는 장기로서 전신에너지 대사의 중심 장기이다. 따라서 인체 골격근의 비중, 골격근 활성도는 혈당 및 혈중 지방산의 이용에 영향을 크게 미치므로 간조직의 병리에도 관여한다. 한편, 간은 위장관으로 흡수된 에너지원이 최초로 통과하는 장기로서 에너지원 변화를 가장 먼저 인식하여 세포 내 에너지 대사를 조절함으로써 전신 대사장기의 에너지원 공급 및 배분을 조율하는 장기이다. 따라서 비만 또는 당뇨병 등 에너지원 과잉 섭취에 따른 대사질환에서 간의 대사기능 저하 및 이에 수반되는 세포손상은 다른 장기보다 선행될 수 있다. 체내 항상성을 유지하기 위하여 간과 골격근은 신호를 교환한다. 골격근 활성이 감소할 경우 체내에서 소비되지 않은 잉여 영양분은 고혈당과 고지혈증으로 나타나며, 이는 간을 포함한 대사장기에서 신호 인식의 변화를 일으켜 비알콜성 지방간증 및 지방간염의 진행을 촉진한다. 지방산 인식체계와 조절의 중심에는 LXRα에 의한 지방 생합성을 들 수 있으며 지난 20여년간 이와 관련된 연구가 체계적으로 수행되었다. 실제 LXRa및 이와 연계되는 지방산 합성의 핵심효소를 제어하는 후보 약물이 현재 연구되고 있으며, 일부는 임상 단계에 있다.

체내 잉여 에너지원의 증가로 인한 고혈당과 고지혈증은 LXRα등 핵수용체 이외에도 세포 표면 신호도 영향을 주는데 상대적으로 이 분야 연구는 최근 주목되었다. 세포 표면 신호계는 진화상 가장 폭 넓고 다양하게 발달되었고, 약물 타겟인 G protein coupled receptor (GPCR)이 대표적이다. GPCR 리간드 자극은 heterotrimeric G proteins를 경유하여 세포 내로 신호를 전달하며, 그 중에서도 특히 Gα protein을 중심

으로한 신호 전달계가 핵심적이다. Gα protein은 4개의 주요 패밀리(Gs, Gq, Gi, G12 family)로 구분되며, 진핵세포의 경우 진화적으로 발달한 많은 GPCR (약 800)의 리간드 자극을 인식, 증폭, 제어하는 신호변환(transducer)의 역할을 수행한다. 따라서 표면수용체의 자극은 이들 transducer의 양이 많고 적음에 따라 다른 강도로 세포 내 신호를 전달한다. 즉 Gα protein은 세포 표면의 다양한 GPCR 자극을 통합하고 신호를 수집/제어하는 중심 분자로 작용한다. 현재까지 에너지 대사에서 G단백질의 역할은 간 또는 췌장 베타세포에서 Gs 및 Gi의 인슐린 신호와 당 대사조절 기능에 관해 보고된 바가 있다. 그러나 여러 G단백질 중 G12 family의 G12/G13에 의한 대사조절 연구는 미진하였다.

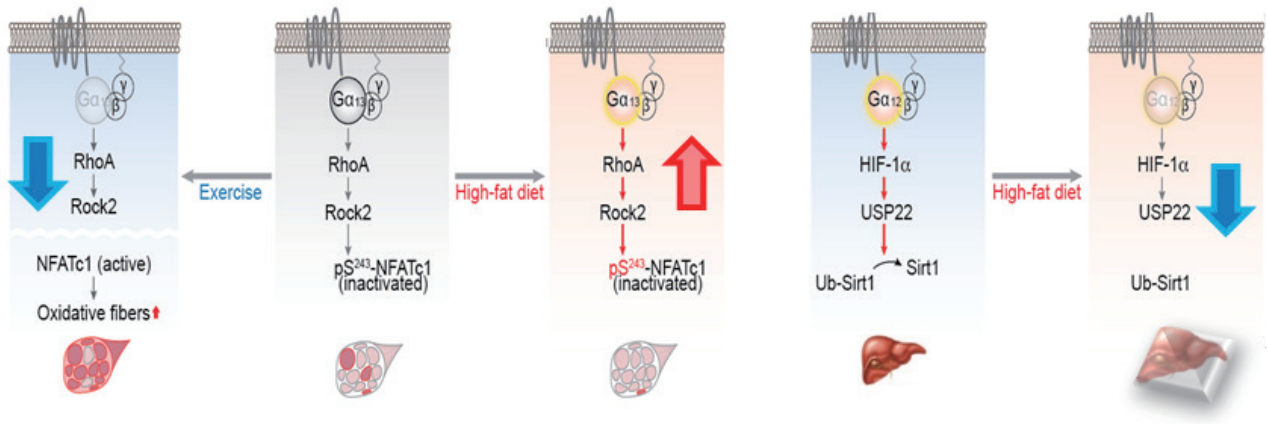

그림 1. G12/G13 조절계에 의한 에너지 대사의 신호 회로

본 연구실에서는 분자생물학, 동물 및 세포 모델을 활용하여 골격근 조직에서 Gα13의 기능을 연구하여 골격근 특이적으로 Gα13 유전자를 제거할 때 근섬유의 유형이 변환되는 사실을 발견하였다. 골격근섬유는 비산화형과 산화형으로 구분하는데, 산화형 근섬유는 미토콘드리아 호흡을 왕성히 수행하므로 지방산 산화를 촉진하고 산소 소비를 증가시킨다. 동물 및 세포 모델에서 Gα13 유전자를 제거했을 때는 근섬유가 비산화형에서 산화형으로 전환되어 미토콘드리아 호흡이 항진되었다. 골격근은 생체의 40-50%가량을 차지하므로 이러한 변화는 전신 에너지 대사를 증진하여 고혈당의 개선, 근육조직의 당과 유리지방산 이용을 증진하였다. 간조직에서는 고지방식이로 유발되는 지방간증을 소멸시켰으며, 이로 인하여 간무게의 정상회복, 조직병리학적 개선도 관찰할 수 있었다. 운동으로 인한 근육활성화는 Gα13 발현을 감소시켰으나, 고지방식이, 당뇨병 상태는 역으로 Gα13 발현을 증가시켰다. 이는 당뇨환자의 근육에서도 확인되었다. G13 감소는 NFATc1 활성을 증가시켰으며, 산화형 근섬유로의 전환을 촉진하였다. Gα13 회로는 RhoA-ROCK2를 매개한 NFATc1의 Ser243인산화를 증가시키며, 운동 자극은 이 과정을 억제함으로써 NFATc1의 핵내 유입과 전사활성화를 자극하여 미토콘드리아 생합성, 산소호흡, 지방산 산화에 관여하는 유전자군을 유도하였다. 그 결과로 산화형 근섬유로의 전환이 촉진되었다. 주목할 만한 사항으로는 골격근의 Gα13을 제거하거나, 고지방식이로 Gα13 발현을 감소시킬 때는 Gα12 발현이 역으로 증가하는 것이었다 (loss of gene 에 의한 gain of function매개 가능성). 본 연구실은 후속 연구로서 Gα12의 역할을 연구하였다. Gα12 는 간을 비롯하여 거의 모든 조직에서 풍부한 발현되는 분자이다. 고혈당 등 대사장애 상태는 간조직의 Gα12 발현을 감소시키며, 이는 지방, 골격근 조직에서도 관찰되었다. 분자적으로는 Gα12는 sirt1을 안정화시켜 미토콘드리아의 생합성과 활성을 증진하는 조절자이며, 이 과정에는 HIF-1α의존적 USP22 전사 발현이 관여하였다. GPCR-G12회로를 자극하는 리간드를 단일로 특정하기는 어려우나 절식 및 재식이 동물모델 연구에서 절식 시는 혈중 adenosine 함량이 증가하였고, adenosine 자극은 adenosine 수용체 4종이 Gα12와 연계됨은 연구하였다. 종합하면, 혈당 등 혈중 에너지원의 감소는 adenosine을 증가시키고, adenosine 자극은 간, 지방조직, 골격근 세포 표면의 GPCR수용체를 통하여 자극을 일으키는데 이때 Gα12발현이 높을 경우 수용

체 신호를 증폭하고 이는 SIRT1, PGC1α, PPARα 등 core complex분자를 활성화 시킴으로써 미토콘드리아 생합성을 자극하였다. 즉 Gα12의 증가 발현은 ATP 생산의 적응 반응을 유도하는 것으로 해석한다. 고지방식이등 에너지원의 과잉 섭취는 반대로 Gα12 발현을 감소시키고, 미토콘드리아 생합성과 산소 호흡을 감소시켜 연료 소비를 줄이는 악순환의 고리에 관여한다. 따라서 NAFLD환자 간조직을 분석하였을 때 정상 또는 단순 지방간과 비교할 때 NASH환자에서는 Gα12발현이 억제되었다. 본 연구의 결과는 지방간, 지방간염은 물론 대사질환의 병리기전을 이해하는 새로운 회로 발견의 의미는 물론 NAFLD치료를 위한 후보 약물의 기전과 개발 성공가능성을 평가할 때 함께 고려해야 하며, 나아가 신약 도출의 새로운 전략에도 활용할 수 있을 것으로 기대한다.

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The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 2: Friday, June 21, 2019 (08:30-09:30)
ROOM A [1F] 103-105 / 108-110

Symposium 1

Non-Alcoholic Fatty Liver Disease and Alcohol-Related Liver Disease

Chairs:

Dong Joon Kim (Hallym Univ.)
Yong Kyun Cho (Sungkyunkwan Univ.)

Fecal Microbiota Transplant in Alcoholic Hepatitis

SM Shasthry

Institute of Liver and Biliary Sciences, India

The current standard of care for severe alcoholic hepatitis (SAH) has several limitations. Only about a third of patients with SAH are deemed to be eligible for steroid therapy (the standard of care). Additionally, steroids have their own limitations – a. their effect on long term (beyond 28 day) survival is doubtful b. over a third of patients do not respond to steroids (as determined by Lille score) c. large chunk of patients who are ineligible to steroids at baseline do not have any definitive options as standard of care. So, we have a large gap between the quantum of problem and the available treatment options.

Gut-derived microbial LPS, a component of the outer wall of gram-negative bacteria, has been known to have a central role in the pathogenesis of ALD. Alcohol has been known to cause dysbiosis and as well disrupt the gut barrier function, consequently, promoting the translocation of microbial LPS from the lumen of the intestines to the portal vein, where it travels to the liver. In the Kupffer cell, LPS binds to CD14, which combines with toll-like receptor 4, ultimately activating multiple pro-inflammatory cytokine genes. Therefore, probiotics, prebiotics, antibiotics, or transplantation of gut-microbiota may be proposed as possible treatment avenues for AH, by attenuation of the increase in LPS or normalizing the healthy gut flora.

Recently, fecal microbiota transplantation (FMT) has been successfully used in the treatment of life-threatening infections with Clostridium difficile. Gut bacteria being actively involved in the pathogenesis of alcoholic hepatitis, FMT might have a potential role in the management of alcoholic hepatitis. Results from the mice study have proven beyond doubt regarding the utility of transfer of fecal microbiome from alcohol resistant mice into the alcohol sensitive mice in preventing the liver injury from alcohol. Pilot studies from our institute (ILBS) have confirmed the benefits of FMT from healthy donor to the severe alcoholic hepatitis patients (who were ineligible to the SMT) with improved short term and as well as long term survival. Further studies addressing the head to head comparison of steroid vs FMT are ongoing. These data from the preliminary clinical trials at our center have heightened our hopes on the utility of FMT in managing this very difficult to manage group of patients with severe alcoholic hepatitis. FMT and/or gut microbial modulation might change the way SAH patients are managed and might increase the hopes of this particularly difficult to treat and sick group of severe alcoholic hepatitis.

Systemic Manifestation in Non-Alcoholic Fatty Liver Disease

Donghee Kim

Stanford University School of Medicine, California, USA

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic fat accumulation either by histology or by imaging after the exclusion of other causes of hepatic steatosis such as viral hepatitis, significant alcohol consumption, a medication known to produce hepatic steatosis or the different causes of liver disease. NAFLD encompasses a broad spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and eventually end-stage liver disease including cirrhosis and hepatocellular carcinoma. The increasing incidence of type II diabetes and obesity is leading to an increased prevalence of NAFLD, with an estimated prevalence of 20-30% in the world. The increasing prevalence of NAFLD is particularly worrying because subjects with NAFLD appear to have higher mortality from non-liver related as well as liver-related death compared to the general population. A recent large population study which consisted of 11,154 subjects in the National Health and Nutritional Examination Survey III shows that simple steatosis was not associated with higher mortality risk after a median follow-up of 15 years. Further analysis shows that NAFLD patients without advanced fibrosis do not have a higher mortality risk and mortality increases as fibrosis advances. These increases in mortality were almost entirely from cardiovascular causes. To sum up these results, cardiovascular disease is the most common cause of mortality in NAFLD and NASH.

Because of well-known association with metabolic comorbidities, NAFLD is commonly associated with obesity, type II diabetes, dyslipidemia, and metabolic syndrome. NAFLD and its comorbid conditions extend well beyond the liver. It is a multisystem and systemic clinical disease entity or syndrome with extrahepatic manifestations These findings have emerging concerns that NAFLD may be a new, and an added risk factor for extra-hepatic diseases such as cardiovascular disease, chronic kidney disease, thyroid dysfunction, sleep disorder, psoriasis, type 2 diabetes mellitus, and polycystic ovarian disease. Indeed, the most common causes of mortality in subjects with NAFLD are cardiovascular disease, followed by malignancy, and liver-related complications at a distant third.

Update on the Management of Non-Alcoholic Fatty Liver Disease

Vincent Wong

The Chinese University of Hong Kong, Hong Kong

Currently, lifestyle intervention, vitamin E, pioglitazone and bariatric surgery (for morbidly obese patients) are available treatments for nonalcoholic steatohepatitis (NASH). Nonetheless, they are limited by applicability, efficacy and potential side effects. As a result, the medical field is actively developing new treatments for this emerging disease. Five drugs (obeticholic acid, elafibranor, selonsertib, cenicriviroc and resmetirom) have entered phase III development, and a number of agents are being tested in phase I and II trials. These agents act via diverse mechanisms ranging from metabolic, anti-inflammatory to anti-fibrotic effects, which would like be necessary for a complex disease like NASH. This would also mean combination therapy is probably required for optimal disease control. In the REGENERATE study, obeticholic acid demonstrated increased rate of improvement in liver fibrosis without worsening of NASH at month 18, and will likely become the first registered drug for NASH. At present, serial liver biopsies are still required to evaluate new NASH treatments. This has increased the difficulty and cost of drug development. The development of validated surrogate endpoints will be an important next step. Finally, Asians remain underrepresented in NASH trials. We need to increase our representation in this area to learn how best to manage Asian patients.

DAY 2: Friday, June 21, 2019 (11:10-12:10)
ROOM A [1F] 103-105 / 108-110

Special Lectures with Debates

Can We Discontinue Hepatitis B Virus Therapy? *Pros. vs. Cons.*

Chairs:

Jordan Feld (Univ. of Toronto, Canada)
Henry LY Chan (The Chinese Univ. of Hong Kong, Hong Kong)

Nucleoside Analogue (NUC) Treatment Can Be Discontinued

Chun-Jen Liu

Department of Internal Medicine, Graduate Institute of Clinical Medicine and Hepatitis Research Center; National Taiwan University College of Medicine and Hospital, Taiwan

Treatment indication and stopping rules are different between patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) versus patients with HBeAg-negative CHB. Unlike patients with HBeAg-positive CHB, there are no clearly defined treatment endpoints (stopping rule) for those with HBeAg-negative CHB. Current treatment guidelines recommend long-term oral nucleos(t)ide analogue(NUC) therapy until immunological control is established, which is characterized by HBsAg seroclearance. Usually, premature withdrawal of NUC leads to virologic and even clinical relapse in more than half of the patients. Our recent data demonstrated that of 100 patients discontinuing 3-year entecavir (ETV) or tenofovir (TDF) therapy, patients discontinuing TDF exhibited significantly higher rates of virologic relapse (52.9% vs 6.1%; $P < .001$) and clinical relapse (15.2% vs. 1.5%, $P=.007$) at 3 months than those discontinuing ETV, but relapse rates at 12 months were comparable. The HBV DNA 1 month after NUC treatment cessation was an early predictor of subsequent relapse. Interestingly, recent data further suggest that exposure of viral antigens to host immune system post-withdrawal may trigger immune control which in some patients fortunately results in HBsAg loss. This favorable event occurs in around 20% of the patients nearly 3 years after stopping NUC. The rate of HBsAg loss was found to be even higher in those who did not receive NUC therapy after developing clinical relapse than in those who started NUC therapy for hepatitis activity. Thus, we believe that NUC treatment may be stopped in a proportion of patients after receiving NUC therapy. Notably post-treatment safety monitoring should be established, and retreatment should be initiated as clinical indicated. Further large studies are needed to validate the value of stopping NUC and to identify the biomarkers that can accurately predict the patients who benefit from finite therapy.

NUC Treatment Should Be Continued

Young-Suk Lim

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The ultimate goal of treating CHB is the prevention of cirrhosis, HCC and immature death in a long-term.[1] However, these clinical outcomes need decades to be evaluated. And thus, intermediate surrogate endpoints, including biochemical, virologic, serologic, and histologic markers, are commonly used to determine treatment response and when treatment can be stopped.

With the availability of highly potent antiviral drugs, entecavir and tenofovir, the virologic response can be achieved in almost all patients as many real world studies have shown. With these drugs, the risk of resistance and safety concern is minimal during long-term treatment. Even in the patients with preexisting multiple drug resistant HBV, the use of tenofovir could induce virologic response in almost all patients, as our two clinical trials have shown.[2-5]

A systematic review also showed that long-term treatment with antiviral agents can improve clinical outcomes, in terms of hepatic decompensation and mortality as consistently demonstrated by randomized controlled trials and observational studies. Nonetheless, the risk of HCC persists even with long term treatment.[6]

Thus, the clinical benefits of current long-term nucleos(t)ide analogue (NA) is as follows:

- Marked decrease in mortality by hepatic decompensation
- Modest decrease in HCC risk
- Stabilizing hepatic function and improved quality of life
- Less need for frequent monitoring

After achieving HBsAg seroclearance during nucleos(t)ide analogue (NA) therapy, the long-term outcome of patients was very favorable with significantly lower mortality and HCC incidence compared to those without HBsAg seroclearance.[7] The problem is that the rate of HBsAg seroclearance was too low. In our Korean cohort of patients, it was only 0.3% per year. In a modeling study for patients receiving NA therapy, the decline in HBsAg titer was very slow, and the median time needed to clear HBsAg was calculated to be 52 years.[8]

Thus, two most important unmet clinical needs with current long-term nucleos(t)ide analogue (NA) is as follows:

- Very low rate of HBsAg seroclearance
- Persistent risk of HCC

The idea of NA discontinuation is focusing on the potential improvement in HBsAg seroclearance rate. However, the clinical benefit of NA discontinuation is unclear. The outcomes of patients after NA discontinuation in many studies may be summarized as follows:

- Statistically higher rate of HBsAg seroclearance:
  - 39.4% (Caucasian cohort, HBV GT D 100%) during up to 6 years of follow-up[9]
  - 19% (Caucasian trial, HBV GT D 85%) during up to 3 years of follow-up[10]
  - 13% (Taiwan cohort, HBV GT B 80%) during up to 6 years of follow-up[11]
  - 2% (Systematic review of 25 studies including 1716 patients)[12]

- Virologic relapse (HBV DNA >2000 IU/mL) >75%12-14
- Clinical relapse (VR + ALT >x2 ULN) >60%[12-14]
- No reduction in HCC risk[11,15]
- Decompensation or death: about 4%[11,14]
- Unable to discriminate beneficial flares from severe potentially risky flares
- Necessity of very frequent monitoring q 2-4 weeks[10]

In conclusion, we have to consider following points when stop NA in CHB Patients:

- Statistically enhanced chance of HBsAg seroclearance
- Clinically unsatisfactory HBsAg seroclearance rate, esp. in Asian patients with HBV genotypes other than A/D
- Need to monitor very frequently and strictly
- Short-term risk: Potential risk of liver failure and death by acute liver failure
- Long-term risk: Unknown risk of HCC and cirrhosis with persistent viremia
- High rate of virological relapse and need to retreat without plateau up to 3 years after Tx D/C
- No reliable D/C criteria
- No reliable biomarker to predict HBsAg seroclearance
- No large-scale unbiased data
- No standard re-Tx criteria
- Unknown cost-effectiveness

Therefore, treatment discontinuation should be considered only in patients without cirrhosis or advanced fibrosis who can be followed closely with ALT and HBV DNA every 2 weeks at least during the first 6 months, and well understand the risk of acute liver failure and death.

It is important always to keep in mind that the physician's first responsibility is "first, do no harm !". Clinical outcomes (risk of acute liver failure and death) should not be jeopardized to achieve intermediate surrogate endpoints (HBsAg seroclearance).

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The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 2: Friday, June 21, 2019 (13:30-14:00)
ROOM A [1F] 103-105 / 108-110

State-of-the-Art Lecture 1

Chair:
Dong Jin Suh (KMP Healthcare Seoul Clinic)

Hepatitis B Virus: From Control to Cure

Jia-Horng Kao

Division of Hepatology and Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital, Taiwan

Although hepatitis B virus (HBV) has been discovered for more than half a century with the availability of effective hepatitis B vaccines for over 3 decades, chronic HBV infection continues to be a major global health problem. It is estimated that there still exist 257 million HBsAg-positive individuals worldwide. Several host, viral, and external factors are identified to predict the progression of liver disease to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) in patients with chronic HBV infection. Nowadays, HBV-related disease progression can be controlled by effective treatment but a cure for chronic hepatitis B (CHB) remains a challenge. Currently approved antiviral agents for CHB therapy include direct antiviral nucleos(t)ide analogues (NUC) and immune modulatory interferon (IFN). Long-term NUC therapy profoundly suppress HBV replication through inhibition of viral reverse transcriptase/polymerase. However, viral relapse frequently occurs after discontinuation of NA in both HBeAg-positive and –negative CHB patients, primarily because of the persistence of intranuclear HBV covalently closed circular DNA (cccDNA). In contrast, despite IFN has dual effects of direct inhibition of viral replication and indirect enhancement of host immunity against the virus, the overall viral response to a finite duration of interferon therapy is far from satisfactory. To reach the goal of eliminating HBV infection, both preventive strategies and effective treatment of HBV infection are essential. First, interruption of HBV transmission routes is the most cost-effective way to reduce the global burden of HBV infection. Combining of hepatitis B immunoglobulin (HBIg) and hepatitis B vaccine as immunoprophylaxis in newborns has been shown to remarkably reduce the rate of mother-to-child transmission (MTCT). However, the implementation of immunoprophylaxis has a failure rate of 10 to 30% in infants born to mothers with an HBV DNA level of more than 200,000 IU/mL. To overcome the gap, a short-term tenofovir therapy for highly viremic pregnant mothers has been implemented as the standard of care to prevent HBV transmission. Second, treating those who are already infected with HBV would decrease the risk of transmission to others and the development of long-term disastrous clinical outcomes. From now on, HBsAg loss with or without the gain of anti-HBs has been recognized as a "functional cure" for HBV and serves as an ideal treatment endpoint. Nevertheless, it is rare to achieve this ultimate goal by using current treatment modalities. To this end, several novel strategies to clear HBsAg have been proposed. Among them, killing of HBV-infected hepatocytes via cytotoxic T cell (CTL) induced by immunotherapy is the most promising one. Although HBV-specific CTL response is vigorous and multi-specific during acute HBV infection, it is usually weak or even undetectable during CHB stage. An ideal immune-therapeutic strategy should combine profound suppression of viral replication to prevent uninfected hepatocytes from HBV infection, which can be achieved by existing NA treatment or novel direct antiviral agents (DAA) with different modes of action, and restoration of HBV-specific CTL response to clear the infected hepatocytes, which can be partially enhanced by host targeting agents (HTA). In summary, despite effective immunoprophylaxis and anti-HBV treatment, chronic HBV infection may remain a major threat in different parts of the world for a long time. Challenges ahead for the global control of HBV infection include the suboptimal coverage of universal vaccination in developing countries, a large number of chronic carriers are undiagnosed and many patients have limited access to treatments in highly endemic areas. All these barriers need to be overcome to eradicate HBV infection. Furthermore, an effective and simple treatment strategy should be implemented to reach the goal of HBV cure by 2030.

DAY 2: Friday, June 21, 2019 (14:00-15:30)
ROOM A [1F] 103-105 / 108-110

Symposium 2

Hepatitis B Virus

Chairs:
Kwan Sik Lee (Yonsei Univ.)
Jong Eun Yeon (Korea Univ.)

Viral Factors for Hepatitis B Virus-Related Hepatocellular Carcinoma

Jeong Won Jang

Department of Internal Medicine, The Catholic University of Korea, College of Medicine, Seoul, Korea

Hepatocellular carcinoma (HCC) is the commonest primary cancer of the liver. It is actually the 5th cancer worldwide and the 3rd leading cause of death. According to the National Statistical Office, the mortality rate of liver cancer in Korean population was 20.9/100,000 in 2017, ranking second after lung cancer with the corresponding rate of 35.1/100,000 in the first place. Despite a significant reduction in the prevalence of HBV infection among the young population, liver cancer mortality and morbidity rates are showing a slight increase in this country, suggesting that this is not because the burden of liver cancer disease is decreasing, but because the whole population in Korea is aging.

As its incidence continues to rise worldwide, identification of risk factors is essential so that HCC would be diagnosed at an early stage and curative treatment could be opted. In general, HCC typically develops in patients with one or more risk factors. The single largest risk factor in the development of HCC is cirrhosis of any etiology, which is present in approximately 80% of those who have primary liver cancer. Chronic HBV infection or HCV infection with advanced fibrosis follow cirrhosis as a cause of HCC. On the other hand, nonviral cirrhosis-related factors (autoimmune diseases, metabolic diseases, etc) or environmental factors (heavy alcohol consumption, cigarette, aflatoxin, etc) can also lead to the development of HCC.

A number of viral factors contribute to HBV-related hepatocarcinogenesis. Among them, high HBV DNA levels with active inflammation have been shown to independently increase the risk of HCC in chronic HBV carriers. HBV genotypes have been associated with the risk of HCC. Genotypes A and D are most prevalent in African populations; reports indicate that infection with genotype A is associated with an increased rate of HCC. HBV genotype C predominantly infecting Asians, especially Korean patients, is associated with a higher risk of liver cancer than genotype B. A high HBsAg level (>1,000 IU/mL) was reported to be predictive of HCC development among patients with HBeAg-negative disease and low HBV DNA < 2,000 IU/mL.

A multitude of reports have revealed that molecular variants of the HBV genome and HBV onco-proteins can also play a role as a viral factor in inducing liver carcinogenesis. Basal core promotor (BCP) T1762/A1764 mutation is among the most studied variants, showing the strongest association with HCC development in both Asian and Western studies. Precore mutation (A1896 mutation) was suggested as another mutants associated with HCC in some studies. Also, pre-S deletion of HBV has been associated with the progression of liver disease as well as the development of HCC in chronic HBV carriers. Viral onco-proteins from intrahepatic cccDNA or HBV integration in infected hepatocytes have been reported to drive hepatocyte malignant transformation through the direct oncogenic potential of HBV. Several studies highlighted the considerable importance of HBs protein mutants (pre-S/S variants) as well as C-terminally truncated HBx proteins in tumorigenesis. Integration of HBV DNA into the host genome occurs at early steps of clonal tumor expansion. It contributes to HCC development through cis- and trans-effects or chromosomal instability.

Hepatic carcinogenesis is a complex process with viral, host and environmental factors contributing to chronic inflammation, cirrhosis and ultimately, HCC. Interplay between persistently high HBV viral load, viral genotypes and molecular variants, HBV integration into the host genome, and HBV onco-proteins derived from cccDNA may contribute independently or jointly to the oncogenesis of HBV-related HCC. A better understanding of the HBV viral factors, its molecular mechanisms, and the development of validated biomarkers would facilitate early diagnosis, prognostics as well as therapeutics with new targets for drug interventions in chronic HBV carriers.

Novel Biomarkers in Management of Chronic Hepatitis B

Yasuhito Tanaka

Nagoya City University Graduate School of Medical Sciences, Japan

Hepatitis B core-related antigen (HBcrAg) is a novel serum marker that correlates with intrahepatic hepatitis B virus (HBV) virological markers such as covalently closed circular DNA (cccDNA) and reflected the chronic hepatitis B disease activity in the liver. Although liver biopsy for the quantification of intrahepatic cccDNA and intrahepatic HBV DNA remains the most accurate measurement for viral reservoir, it is limited by its invasive nature, the potential for sampling error and the lack of a standardized assay.

Recently, we apply the droplet digital PCR (ddPCR) method to cccDNA quantification.The cccDNA content was correlated more closely with HBcrAg (R^2=0.862) than HBsAg (R^2=0.652). Importantly, cccDNA content/assay did not change during liver repopulation despite that cccDNA content/hepatocyte was reduced as the number of human hepatocytes increased (unpublished data), suggesting that cccDNA is extremely stable and its elimination may require cell death.

HBcrAg was measured in serum using the Chemiluminescent Enzyme Immunoassay (CLEIA) system for fully automated Lumipulse CLEIA analyzer. As for clinical practice of HBcrAg assay; 1) This marker is helpful in predicting spontaneous or treatment-induced HBeAg seroconversion, sustained response to nucleos(t)ide analogue (NA). Recently, core assembly modulators (CAMs) are developing, and the HBcrAg might be useful for monitoring during treatment among even HBeAg-negative patients. As the introduction of higher sensitive HBcrAg assay was desired, we show here fundamental and clinical information about the newly-developed assay. 2) The HBcrAg level at NA cessation point would be a predictor of non-relapse after cessation of NA therapy (Shinkai N, Tanaka Y, et al. 2007). Based on HBV guideline from the Japan Society of Hepatology, the combination of HBsAg and HBcrAg levels were scored into three groups; the percentage of prediction success was 80–90% in the low-risk group, approximately 50% in the medium-risk group and 10–20% in the high-risk group (Tanaka E, et al. Hepatol Res 2014). 3) HBcrAg is an excellent predictor of hepatocellular carcinoma (HCC) development in chronic hepatitis B patients without NA therapy. HBcrAg was superior to HBV DNA in terms of predictive power for HCC development by time-dependent receiver operating characteristic analysis (Tada T. et al. 2016). HBcrAg is also a predictor of the post-treatment recurrence of HCC during antiviral therapy. Serum HBcrAg and intrahepatic cccDNA suppression by NAs may be important to prevent HCC recurrence (Hosaka T et al. 2010). In conclusion, serum HBcrAg is a convenient and useful marker as a potential surrogate marker of cccDNA in the clinical practice. The higher sensitive HBcrAg could be applied to clinical trials including CAMs.

Introduction

Chronic hepatitis B (CHB) affects approximately 240 million persons worldwide,[1] with an estimated 15%-40% progressing to cirrhosis, decompensation and/or hepatocellular carcinoma (HCC).[2] Currently, hepatitis B virus (HBV) cannot be completely eradicated due to the presence of covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes.[3–5] Therefore, the present goal of monitoring is to ensure a high degree of virological suppression, ideally with hepatitis B surface antigen (HBsAg) seroclearance, leading to biochemical remission,

histological improvement and reduction of the risk of complications.[6,7] Although liver biopsy for the quantification of intrahepatic cccDNA and intrahepatic HBV DNA remains the most accurate measurement for viral reservoir, it is limited by its invasive nature, the potential for sampling error and the lack of a standardised assay. Non-invasive serological markers can be used as surrogate markers of intrahepatic viral replicative activity. Established serological markers include serum HBV DNA levels and serum HBsAg titres, both of which have been shown to predict the risk of cirrhosis and HCC.[8–11] However, as cirrhosis and HCC can still occur in many patients despite undetectable HBV DNA[12] and HBsAg seroclearance,[13,14] any promising markers with predictive value in these scenarios are very much welcome. Moreover, given that almost all patients treated with anti-viral therapy have undetectable HBV DNA, more accurate biomarkers for risk stratification are needed. Recently, linearised HBsAg (HQ-HBsAg) assay achieving an even lower limit of detection for HBsAg[15] has been shown to correlate with serum HBV DNA and HBsAg levels, which makes it a potential marker for stratifying patients with HBsAg seroclearance.[16] Another new marker, the hepatitis B core-related antigen (HBcrAg), has also been advocated as a serum marker for disease monitoring and prognostication of CHB. In this review, the clinical application of HBcrAg in CHB patients based on its virological features, the distinctive profiles in different disease stages and the profile under anti-viral treatment will be discussed.

Current Treatment Strategy: Towards Hepatitis B Virus Cure

Seng Gee Lim

National University of Singapore, Singapore

Future Treatment Strategy: Towards Hepatitis B Virus Cure

Henry LY Chan

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

Understanding of the intrahepatic hepatitis B virus (HBV) replication and trafficking has enabled the development of many new direct anti-viral agents. Many new treatment targets have been identified in recent years targeting to improve the chance of functional cure with a finite duration of therapy. Early clinical data has been promising. Myrcludex B is a myristoylated peptide encompassing amino acids 2-48 of the HBV pre-S1 region, which can specifically interact and block the HBV receptor, sodium taurocholate co-transporting polypeptide, on hepatocytes. RNA interference with siRNA is another strategy; it can block the mRNA and production of HBV antigens from all open-reading frames of HBV. Capsid assembly inhibitors have many potential therapeutic effects, including inhibiting of viral replication, reactivation of host innate immune response and disruption of the cccDNA maintenance.

Immune modulation is another strategy. But early data on toll-like receptor-7 agonist and therapeutic vaccine are not too promising. There is some exciting early data on the use of retinoic acid inducible protein I (RIG-I) agonist, which has a dual mode of action to directly inhibit viral replication and stimulation of type III interferon in chronic hepatitis B patients. In the long run, combination therapy of different antiviral agents is likely needed to achieve functional cure for chronic hepatitis B.

DAY 2: Friday, June 21, 2019 (16:30-17:50)
ROOM A [1F] 103-105 / 108-110

Clinical Hepatology Update

Clinical Trials of Management in Chronic Liver Diseases (*K)

Chairs:
Kwang Cheol Koh (Sungkyunkwan Univ.)
Il Han Song (Dankook Univ.)

Chronic Hepatitis B: Where Are We Now for Functional Cure?

Hyun Woong Lee

Department of Internal Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea

만성 B형간염: Functional Cure를 위해 우리는 지금 어디에?

이 현 웅

연세대학교 강남세브란스병원 소화기내과

Loss of HBsAg with sustained HBV DNA suprresion has been termed functional cure. It also referred to as clinical or immunologic cure for chronic hepatitis B. It is the ideal goal of therapy recommended by current guidelines. It means sustained, undetectable HBV DNA and HBsAg titer with or without anti-HBs, but with the persistence of residual cccDNA, and the absence of spontaneous relapse after the cessation of treatment. However, current nucleos(t)ide analogues and pegylated interferon offers limited capability in achieving functional cure. The major cause is the lack of available drugs to eliminate cccDNA and integarated HBV DNA, and restore innate and adaptive immunities against hepatitis B virus. Current nucleos(t)ide analogues just suppress the viral load and pegylated interferon slightly enhance the immunologic response. Although it is not perfect, current potent antiviral agents with pegylated interferon combination therapy as well as selection of patients (with low viremia and low HBsAg titer) might be considered to achieve functional cure.

In the near future, antiviral agents targeting various steps of the HBV life cycle, including HBV entry (NTCP inhibitor), HBV cccDNA production and processing (cccDNA inhibitors), viral replication and viral protein expression (capsid assembly modifiers, RNA interference, Nucleic Acid Polymers, etc.) have entered preclinical or early clinical evaluation.

New combination of antiviral agents with immunomodulators might reactivate the host immune system and eliminate cccDNA and integrated HBV DNA to a complete cure of HBV infection.

1. Functional Cure의 정의

최근 만성 C형간염이 새로운 경구용 항바이러스제의 개발로 인해 2030년 C형간염 완치 및 박멸이라는 캠페인이 시작되면서, B형간염도 완치를 위한 새로운 치료법 개발을 위한 노력이 시작되었다.

B형간염의 완치란 혈액내의 HBV DNA, HBsAg의 소실과, 간조직내에 cccDNA 및 숙주 유전자에 integrated HBV DNA의 완벽한 소실을 의미한다.[1,2] 그러나 현재로서는 이러한 목표를 성취하기가 어려워 그 다음으로 제시된 목표가 바로 functional cure를 의미하는 혈액내의 HBV DNA, HBsAg의 소실 (anti-HBs 존재 유무와 상관없이)이다.[1,2] 비록 cccDNA가 존재하지만, 치료 종료 후 재발이 없으며, 간 손상이 진행하지 않고 간경변증이나 간세포암의 위험이 감소하는 것을 의미한다. 즉, 만성 B형간염의 성공적인 면역학적 조절 상태로 이는 급성 B형간염의 완치와 유사한 개념이라 하겠다. 그러나, 이러한 functional cure도 성취하기 어렵기 때문에 임상에서는 주로 혈청내 HBV DNA 음전상태를 유지하고 간기능 검사의 정상화가 유지되는 것만으로도 좋은 치료 반응으로 평가하고 있어, 이러한 목표는 성취하기 쉽지만 임상의로서 전혀 만족스럽지 못한 목표이다.

2. 완치를 위한 도전의 어려움

B형간염의 만성화는 바이러스 요인 뿐만 아니라 숙주요인도 동반하기 때문에 접근이 어렵다. HBV 유전자는 숙주 간세포의 핵 내로 침범하여 episomal minichromosome의 형태,이른바 cccDNA로 존재한다. HBV DNA의 일부 조각은 숙주의 유전자와 결합하며 cccDNA와 함께 바이러스 전사를 조절하면서 바이러스 복제에 유리한 세포내 환경을 만들어 간다. 특히 cccDNA는 간세포내에 안정적으로 존재하면서, 생존기간이 길어서 새로운 virion이 들어오지 않아도 스스로 재충전이 가능하며, 다양한 HBV DNA 조각이 숙주 유전자와 결합하여 완치를 위한 도전을 어렵게한다.[3-5]

여러 연구에서 밝혀진 대로, 바이러스 항원이 선천면역반응을 억제하고, HBV 특이 B세포의 기능을 손상시키며, 높은 농도로 유지되는 바이러스 항원이 결국에는 HBV 특이 T세포의 기능적 무력화를 유도한다고 알려져 있다. 특히 HBsAg은 episomal cccDNA와 S gene의 필수요소들이 잘 들어 있는 integrated HBV DNA 조각에 의해서 만들어지기 때문에, 숙주의 항바이러스 면역체계를 잘 유도한다면 cccDNA나 integrated HBV DNA 조각을 모두 제거하지 못하더라도 우리가 얻고자 하는 임상적인 목표인 functional cure를 성취할 수 있다. 또한 결함이 발생한 면역세포의 기능을 강화하고 회복하게 해 줄 수 있는 약제가 개발된다면 궁극적인 목표인 cccDNA나 integrated HBV DNA를 제거할 수 있다. 하지만, 현재로서 이러한 약제의 개발이 요원하여 선택된 환자들을 대상으로 기존 약제들의 병합요법에 대한 연구가 진행되고 있다.

3. 현재 약제들의 한계

경구용 약제들은 투약의 편의성과 복약 순응도가 높아 널리 사용되고 있지만, 강력한 항바이러스제로 알려져 있는 entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide 조차도 cccDNA를 직접 타겟으로 개발된 약제가 아니다. 따라서, 장기간의 항바이러스제의 투약이 필요하며, 특히 HBeAg 음성 환자에서 약물을 종료하기가 어렵다. 결국 전 생애기간동안 약물을 투약해야 한다는 부담감은 약제 부작용에 대한 대책과 함께 단기간 치료제에 대한 개발을 요구한다.

이에 반해서 pegylated interferon은 숙주의 면역세포을 활성화하며, 항바이러스효과를 보이는 단백질을 코딩하는 interferon stimulated genes의 생성을 유도한다. 이 기전을 통해 pegylated interferon은 HBV 전사를 억제하고 pregenomic RNA와 core particle의 파괴를 유도하며, cccDNA의 후생 유전 조절 (epigenetic regulation)을 통해 바이러스 항원의 생성을 감소시킨다. 이러한 기전 때문에 치료기간이 정해져 있으며 명백히 혈청 HBsAg 양의 감소와 치료 종료 후 반응의 유지를 관찰할 수 있다. 그러나 이런 효과를 보이는 환자의 비율이 적고 부작용으로 인해 임상의사들의 처방 빈도가 낮다.

결국 cccDNA이나 integrated HBV DNA 조각을 제거하고, HBV에 대한 면역 관용상태를 해제하는 것이 만성 B형간염 치료를 위한 열쇠가 될 것이다. Nucleos(t)ide analogue 또는 pegylated interferon 단독으로는 간세포 핵 내에 존재하는 cccDNA 제거에는 제한된 효과만 가지고 있어 functional cure를 획득하기도 어렵다. 그러나 두 약제를 적절히 조합할 경우에는 (De novo combination, sequential combination strategy) pegylated interferon의 장점인 선천면역을 조장하여 $CD56^{brihgt}$ NK 세포의 활성을 유도하고 장기간의 nucleos(t)ide analogue 치료의 장점인 HBV 특이 T세포의 활성 회복과 증식을 통한 적응면역의 활성화로 HBsAg 감소를 이끌어 functional cure을 획득할 수 있다.

4. Functional cure의 새로운 예측 인자

Anti-HBc 정량법이 HBeAg 음성 만성 B형간염 환자에서 functional cure의 예측인자로 이용될 수 있으며, HBV core antigen, HBeAg, 그리고 22-kDa precure 단백질을 측정하는 HBV core-related antigen (HBcrAg)이 간내 cccDNA 수치와 상관관계가 있음이 보고되었다. HBsAg 수치와 HBcrAg 수치를 이용하여 약제 중단 후 재발의 예측인자로 사용가능함을 보고하였다. 최근에는 혈청에서 encapsidated pregenomic RNA를 측정할 수 있어 HBV RNA로 명명하고 간내 cccDNA의 전사 활동도를 반영하는 표지자로 사용될 수 있음을

보고하였다. 혈청 HBV RNA를 이용하여 항바이러스제 치료시 HBeAg 혈청 전환의 예측인자로, 항바이러스제 중단 후 HBsAg 재양전의 예측인자로 사용될 수 있다고 보고하였다.[6,7]

요약하면, 현재 사용되고 있는 항바이러스제 단독으로는 functional cure를 획득하기도 쉽지않다. 최근 HBV 생활사를 단계별로 겨냥하며 만들어진 새로운 약제, HBV entry (NTCP inhibitor), HBV cccDNA inhibitors, capsid assembly modifiers, RNA interference, Nucleic Acid Polymers 들이 임상연구 중이다.[8] 머지않은 미래에 새로운 약제들의 조합으로 숙주의 면역세포 능력의 회복과 바이러스 증식억제를 통해 cccDNA와 integrated HBV DNA 조각을 제거하여 궁극적인 완치까지 상상해 본다.

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Non-Alcoholic Steatohepatitis: Key Targets and Endpoints

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Non-alcoholic fatty liver disease (NAFLD) has diverse spectrum ranging from non-alcoholic fatty liver (NAFL) with only intrahepatic deposition to fatty deposits, to non-alcoholic steatohepatitis (NASH) with hepatocyte ballooning, inflammation and various stages of fibrosis, and finally cirrhosis. NAFLD is the most common cause of liver disease in western countries. In Korea, the prevalence of NAFLD diagnosed by abdominal ultrasonography is 16-33% and the prevalence is increasing.

NAFLD and NASH are chronic diseases that progress slowly, and it is very difficult to identify all-cause mortality, which are the endpoints of other common clinical studies. It is also difficult to identify liver related mortality, including complications of liver cirrhosis and the occurrence of hepatocellular carcinoma. Therefore, surrogate endpoints may be used instead for clinical studies in these chronic diseases.

According to the U.S. Food and Drug Administration (FDA), these surrogate endpoints are "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict benefit "on irreversible morbidity or mortality. Recent studies have shown that histologic features that have the greatest impact on mortality among patients with NASH were the presence of significant fibrosis. According to the natural history of NAFLD, NAFL has a low fibrogenic potential, while NASH progresses to advanced fibrosis and is known to be associated with more advanced metabolic diseases. Among the pathologic findings of NASH, inflammation and hepatocellular ballooning are known to be associated with fibrosis progression. Inflammation, hepatocellular injury is a disease activity that leads to progression of fibrosis to cirrhosis. And the degree of fibrosis means the stage of disease, which means to what extent cirrhosis has already been reached. Therefore, appropriate endpoints should be set according to which one of them is targeted. Surrogated endpoints are resolution of NASH without worsening of fibrosis or improvement in fibrosis without progression of steatohepatitis. These endpoints are based on repeated liver biopsy findings, making it difficult to perform large-scale, long-term clinical studies. In addition, if the above mentioned endpoints are reached, it is necessary to confirm whether the mortality caused by NASH is reduced. A number of new drugs are currently under clinical trials targeting these endpoints, and the results of these studies are expected to be reported in the near future.

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Cirrhosis: Effort against Fibrosis and Portal Hypertension

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간경화: 간섬유화 및 문맥압 항진증 치료

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The pathophysiology of decompensation in cirrhosis involves portal hypertension, bacterial translocation followed by systemic inflammation resulting in splanchnic arteriolar vasodilation and circulatory dysfunction. The mainstays of treatment for cirrhosis are targeted against key factors of pathogenesis of decompensation. Reducing portal hypertension by non-selective beta-blockers, targeting intestinal dysbiosis and bacterial translocation by rifaximin, improving circulatory dysfunction by long-term albumin administration and decreasing the systemic inflammation by statins have shown potential benefit to decrease cirrhosis progression. Further studies are warranted to confirm the safety and benefits of these strategies.

Keywords: Cirrhosis, Portal hypertension, Non-selective beta blocker, Statin, Albumin, Rifaximin

서 론

만성적인 간손상은 정상적인 간세포 소실 및 간섬유화를 거쳐 간경화로 귀결되며, 증상이 없는 대상성 간경화는 매년 5~7%에서 비대상성 간경화로 진행한다. 간경화 진행을 억제하는 현재 가장 효과적인 방법은 바이러스, 알코올 등 간손상의 원인을 치료하는 것이며, 아직 간섬유화 자체를 호전시키고 정상 간세포를 회복시키는 입증된 치료법은 없다. 간경화 합병증 발생의 병태 생리에 대한 이해가 깊어지면서, 이러한 병태생리의 각 단계 즉, 장내세균 전이 (bacterial translocation), 순환기능장애 (circulatory dysfunction), 전신 염증 (systemic inflammation), 문맥압항진 등을 치료함으로써 간경화 합병증과 사망을 줄이려는 다양한 시도들이 성공적으로 이루어지고 있다. 이 글에서는 간경화 및 문맥압 항진증의 합병증을 예방하고 치료하기 위한 최신 연구들에 대해 소개하고자 한다.

본 론

1. 비선택적 베타차단제

비선택적 베타 차단제 (non-selective beta-blockers, NSBB)가 내장혈류량 감소를 통하여 문맥압을 저하시킴으로써 임상적으로 의미 있는 문맥압 항진증 (clinically significant portal hypertension, CSPH)과 큰 정맥류를 동반한 간경화 환자에서 정맥류 출혈을 감소시키는 사실은 잘 알려져 있으며, 현재 정맥류 출혈의 1차 및 2차 예방을 위한 표준 치료로 권고된다.[1] 그러나, NSBB를 정맥류가 없는 대상성 간경화 환자에게 투여하였

을 때 정맥류 발생을 예방하는 효과는 입증되지 않았고,[2] 작은 정맥류에서 큰 정맥류로의 진행을 막는 효과도 상반된 연구 결과를 보인다.[3,4] 비선택적 베타차단제와 alpha1 차단제의 성질을 동시에 지닌 carvedilol이 작은 위식도 정맥류의 진행을 늦춘다는 연구가 최근 발표되었다.[5] 또한, 임상적으로 의미 있는 문맥압 항진증(HVPG ^{3}10 mmHg)을 동반한 대상성 간경화 환자에서 NSBB의 장기간 투여가 주로 복수의 발생을 줄임으로써 비대상성 간경화로의 진행 및 간질환 관련 사망률을 낮춘다는 무작위 대조군 전향 연구가 올해 발표되었다.[6] 그러나, 불응성 복수나[7] 자발성세균성 복막염(spontaneous bacterial peritonitis, SBP)을[8] 동반한 비대상성 간경화 환자에서 NSBB가 사망률을 높인다는 연구가 있어 특히 고용량 사용시 주의해야 한다. 미국 및 유럽간학회에서는 불응성 복수나, 혈압저하, 저나트륨혈증, 급성콩팥손상, 패혈증, SBP 등이 발생할 경우 NSBB를 중단할 것을 권고한다.[1,9] 또한 alpha 1 차단 효과가 있는 carvedilol의 경우에는 전신혈압 강하 효과가 현저하여 순환기능장애를 악화시킬 수 있고, 복수를 동반한 간경화 환자에서 사망률을 높인다는 메타연구 결과가 있으므로[10] 복수를 동반한 간경화 환자에서 권고되지 않는다.[9]

2. 스타틴(statins)

스타틴은 항염증 및 항섬유화 효과를 지니며 동물 실험에서 간섬유화를 억제한다.[11] 또한 Rho kinase와 KLF2 발현을 억제함으로써 문맥압항진증을 호전시킬 수 있다.[12] 대부분의 후향 코호트 연구에서 스타틴 사용이 간경화 환자에서 비대상성 간경화 진행 및 사망률을 감소시키는 것으로 보고되었다.[11,13] 몇몇 소규모 무작위 대조군 전향 연구에서 스타틴 투여는 대상성 간경화 환자에게 안전하며 문맥압을 효과적으로 감소시키는 것으로 보고하였다.[14-16] 158명의 정맥류 출혈을 경험한 간경화 환자를 대상으로 한 전향 연구에서 스타틴과 NSBB 동시 투여군은 NBBB 단독 투여군에 비하여 정맥류 재출혈률의 유의한 차이는 없었으나 전체 사망률은 유의하게 낮은 것으로 보고하였다.[17]

3. 알부민

알부민 투여는 간경화 환자에서 대량 복수 천자로 인한 순환기능 장애를 줄이고, SBP시 발생할 수 있는 콩팥기능 이상을 예방한다. 또한 혈관 수축제와 함께 간신증후군 치료에 사용된다.[9] 알부민은 주로 유효 혈장량을 증가시킴으로써 효과를 나타내지만, 항염증 및 항산화 효과도 지닌다.[18] 저나트륨혈증을 동반한 간경화 환자를 대상으로 한 최근의 후향연구에서 알부민 정맥 투여는 저나트륨혈증을 개선하고 30일 사망률을 감소시키는 것으로 나타났다.[19] 그러나, 합병증이 없는 복수를 동반한 간경화 환자에서 알부민 장기 투여가 임상 경과를 호전시키는 지에 대해서는 논란이 있었다.[20] 최근에 합병증 없는 복수를 동반한 환자를 대상으로 알부민을 장기 투여한 무작위 대조군 대조군 연구가 발표되었다. 알부민 투여군은 첫 2주간 주 2회 알부민 40g, 2주 이후에는 주 1회 알부민 40g을 최대 18개월간 투여하였다. 알부민 투여군에서 대조군에 비해 18개월 생존율이 유의하게 높았다(77% vs. 66%, P=0.028).[21]

4. Rifaximin

Rifaximin은 장에서 흡수되지 않는 항생제로 간성뇌증의 2차 예방에 효과가 입증되어 락툴로즈와 병행 투여가 권고되고 있다.[22] Rifaximin의 SBP 예방 효과에 관한 메타분석에서 rifaximin은 norfloxacin이나(오즈비 0.45, 95% 신뢰구간 0.19-0.76) 항생제를 투여하지 않는 것에(오즈비 0.34, 95% 신뢰구간 0.11-0.99) 비하여 SBP 재발을 효과적으로 감소시키는 것으로 나타났다.[23] Rifaximin은 장내 세균총을 변화시키고[24] 장내세균전이를 억제하여 내독소혈증(endotoxemia) 및 혈중 염증성 사이토카인을 감소시킨다.[25] 그러나, 순환기능장애 개선에 대해서는 상반된 결과를 보고하고 있다.[25,26] 국내에서 시행된 후향 코호트 연구에서 rifaximin과 lactulose를 병행 투여한 군이 lactulose 단독 군에 비하여 생존율이 높고 SBP, 정맥류 출혈 및 간성뇌증의 위험이 낮은 것으로 보고하였다.[27] 또한, 간성 뇌증 예방 효과를 평가한 무작위 전향연구를 post hoc 분석한 연구에서 rifaximin이 간경화 합병증을 감소시키고 특히 MELD 점수가 12 이상인 경우 간성뇌증을 제외한 합병증도 감소시키는 경향을 보였다.[28]

5. 기타

반복적인 간성뇌증을 경험한 간경화 환자에서 변이식 (fecal microbial transplant, FMT)의 안정성을 평가하기 위한 1상 연구가 최근 발표되었다. 간경화 환자에서 FMT는 안전하였으며, 십이지장내 미생물 다양성을 회복시키고 혈청 interleukin-6, lipopolysaccharide-binding protein 등을 감소시켰다. 간성뇌증의 재발 빈도에 차이는 없었으나 인지기능 검사 점수가 향상되었다.[29]

비만한 간경화 환자에서 생활 습관 조절을 통하여 체중감량을 하면 문맥압이 의미 있게 감소한다는 연구가 발표되었다.[30] 이 연구에는 바이러스 간염 등 비알콜성지방간염 이외의 간경화 환자들도 포함되었으며, 체중을 10% 이상 감량한 군에서 문맥압 감소는 더욱 유의하였다. (-23.7% vs -8.2%)

결 론

간손상의 원인을 제거하는 것이 간경화의 진행을 막는 현재 가장 중요하고 효과적인 치료이지만, 비대상성 간경화 발병 과정 중 여러 요인을 차단함으로써 간경화의 합병증을 줄이고 생존율을 증가시킬 수 있다. NSBB가 정맥류 출혈 예방 이외에 비대상성 간경화로의 진행 예방에 효과적일 가능성이 있다. 스타틴은 문맥압을 낮추고 생존율을 향상시킨다. 장기간 알부민 투여로 생존율을 향상시킨다는 연구가 발표되었고, rifaximin이나 FMT 등 장내 미생물을 조절하는 치료에 대한 가능성이 제시되고 있다. 그러나, 이러한 치료법의 효과 및 안전성은 간경화의 진행 정도에 따라 달라질 수 있고 아직 대규모 무작위 전향 연구가 불충분하므로 향후 연구를 통한 검증이 필요하다.

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Hepatocellular Carcinoma Treatment Showdown: Mono vs. Combination Therapy

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1. Mono-treatment options for incurable HCC

Current guidelines recommend transarterial chemoembolization (TACE) as the standard therapy for patients at an intermediate (BCLC-B) stage beyond the Milan criteria based on high levels of evidence. TACE with drug-eluting beads (DEB) has been launched with promising results and is increasingly used with less liver toxicity than and at least similar antitumor efficacy to conventional TACE. However, TACE alone is not a treatment method with curative intent, and thus cannot be generally expected to induce perfect therapeutic outcomes. On the other hand, radioembolization has been recently proposed as another modality for intermediate HCC patients, its safety issue regarding reduction in liver function remains to be figured out. Sorafenib is the first agent ever to show a survival benefit in patients with advanced HCC and has now become the standard first-line treatment for patients with BCLC-C stage HCC. Lenvatinib has recently shown to be non-inferior to sorafenib, and accordingly represents an alternative to sorafenib in the first-line setting. For the patients who intolerable or progressed on sorafenib, regorafenib and next cabozantinib exhibited a survival improvement as rescue therapy. A subset of sorafenib-failed patients with serum AFP of ≥400 ng/mL also would benefit from second-line ramucirumab. Although final results are pending, early data on immune checkpoint inhibitors have shown promising signs of therapeutic efficacy in advanced HCC patients.

2. Combination treatment options for incurable HCC

The combinations of local and systemic therapies have been eagerly studied to improve response rate and survival in patients with incurable HCC. Since ischemia and hypoxia induced by TACE would trigger the activation of proangiogenic factors, TACE combined with anti-angiogenic agents may constitute an effective strategy to achieve better outcomes. Disappointedly, a randomized phase II study testing the combination of DEB-TACE plus sorafenib versus plus placebo (SPACE trial) did not demonstrate satisfactory efficacy in terms of time to progression and overall survival in patients with intermediate-stage HCC. Additionally, a recent phase III trial failed to demonstrate a survival benefit of SIR-Spheres combined with sorafenib over sorafenib alone in inoperable patients (SORAMIC trial). As for advanced HCC, clinical benefit with sorafenib monotherapy is inadequately limited with less than 3 months of actual survival gain. Recent studies have carefully suggested TACE-based combinations with radiotherapy or sorafenib as superior tools to the standard sorafenib for fighting against advanced-stage HCC, if tumors would not have metastatic foci. Targeted therapy combined with immune checkpoint inhibitors is also an approach currently under investigation. A phase 1b trial of lenvatinib plus pembrolizumab induced possibly compelling response and progression outcomes in individuals with unresectable HCC. In 2018, the FDA has granted a breakthrough therapy for atezolizumab, an anti-PDL1 inhibitor, plus bevacizumab, a monoclonal antibody against

VEGF, as a first-line treatment for patients with advanced HCC, and a phase III trial (NCT03434379) comparing this combination versus sorafenib is currently ongoing.

3. Conclusions

The management of HCC has evolved considerably over the last decade. As the current scenario of monotherapeutic strategies still remains unsatisfactory against a myriad of refractory HCCs, future challenges would be to evaluate sequential or combination regimens and to incorporate them into clinical management as soon as possible.

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The Liver Week 2019

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Hepatology Associates Course (*K)

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Byung-Cheol Song (Jeju National Univ.)

Treatment of Chronic Hepatitis B and C Virus

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만성 B형간염과 만성 C형간염의 치료

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Chronic hepatitis B and C are the most important etiologies of chronic liver disease in Korea. The ultimate goals of antiviral treatment are to decrease mortality from liver disease and lengthen survival by preventing viral replication and alleviating hepatic inflammation and by preventing the progression of fibrosis, development of liver cirrhosis, and hepatocellular carcinoma. The approaches for antiviral treatment of chronic hepatitis B and C are described for the hepatology associates and they are based on the recently updated guidelines suggested by the Korean associations for the study of the liver.

Keywords: Chronic, Hepatitis, Hepatitis B virus, Hepatitis C virus, Treatment

1. 만성 B형간염

1) 서론

B형간염은 전 세계적으로 3억 5천만 명의 만성 감염자가 있고 매년 60만명 이상이 관련 질환으로 사망하는 중요한 질환이다[1]. 우리나라에서는 1980년대에는 HBV 감염률이 8-10%의 높은 수준이었으나 신생아 예방접종 사업, 국가 예방접종 사업, 주산기 감염 예방사업이 시작되면서 HBV 감염률은 점차 감소하여 2008년 이후에는 꾸준히 3.0% 수준을 유지하고 있다. 그러나 우리나라 만성 간염 및 간경변증 환자의 약 70%[2], 간세포암종 환자의 약 65-75%에서 HBsAg 이 검출되는 점을 고려하면[3], 아직도 만성 B형간염이 우리나라 국민 건강에 미치는 영향은 매우 크다. 만성 B형간염은 감염 후 면역학적 자연경과에서 다양한 소견으로 나타나기에 단 1회의 검사를 통하여 해당되는 임상 단계를 단정짓거나 항바이러스 치료 시작을 결정하는 것이 부적절한 경우가 많다 (Figure 1)[4]. 특히 다른 바이러스에 의한 중복감염, 음주력, 약물 복용력 및 HBV 감염과 간세포암종의 가족력 등에 중점을 둔 병력 청취와 신체 검사가 매우 중요하다.

2) 치료 목적과 목표

만성 B형간염의 궁극적인 치료 목적은 HBV 증식을 억제하여 염증을 완화시키고 섬유화를 방지하여, 간경변증과 간세포암종의 발생을 예방함으로써 간질환에 의한 사망률을 낮추고 생존율을 향상시키는 것에 있다[5]. 그러나 현재까지의 항바이러스 치료제는 치료에도 불구하고 핵 내의 cccDNA가 지속되기 때문에 HBV의 완전 퇴치를 기대하기가 어려우므로 바이러스반응을 장기간 유지하는 것이 중요하다[6]. 이와 같이 치료 목적을 달성하기 위한 임상에서의 목표는 ALT의 정상화, 혈청 HBV DNA 불검출, HBeAg 혈청소실 및 전환, HBsAg 혈청소실

및 전환이다. 특히 HBsAg 혈청소실 및 전환은 B형간염 치료의 이상적인 목표이다.

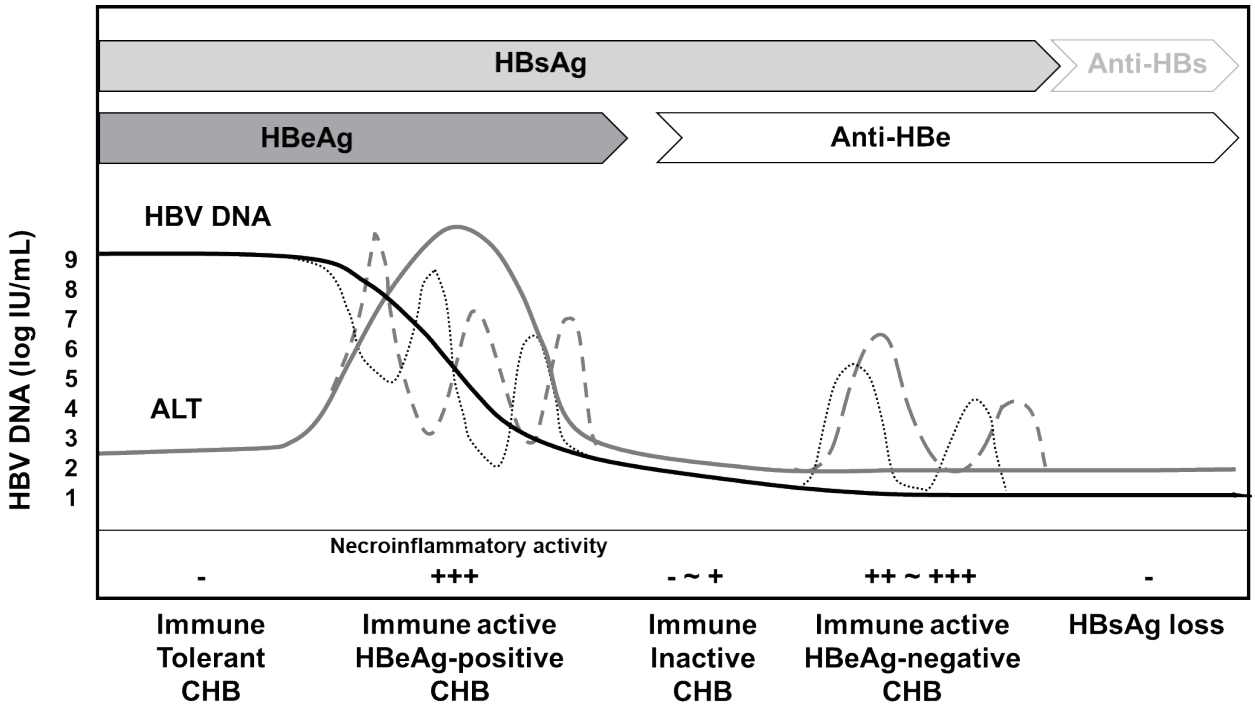

Figure 1. Natural course of chronic hepatitis B[5]

3) 치료 대상과 초기 평가

항바이러스 치료 시작을 결정하는 데에는 크게 1) 간질환의 진행 정도, 2) B형간염 바이러스의 증식 정도, 그리고 3) 간손상의 동반 여부와 같은 요소들을 고려한다(Figure 2). 간질환의 진행 정도는 대상성 또는 비대상성 간경변증 여부를 판단하여야 하며 B형간염 바이러스의 증식 정도는 혈청 HBV DNA PCR 검사를 통하여 확인할 수 있다. 간손상의 동반 여부는 혈청 ALT가 주로 활용되며, 그 외에도 간생검을 통해서 염증괴사 동반 여부를 확인할 수 있다.

4) 치료 약제

2017년부터 국내에서 테노포비어 알라페나마이드 푸마르산(tenofovir alafenamide fumarate, 이하 테노포비어AF)과 베시포비어 디피복실 말레산(besifovir dipivoxil maleate, 이하 베시포비어)이 성인에서 만성 B형간염 치료제로 승인됨에 따라 총 8가지의 항바이러스제를 사용할 수 있다. 약제들은 크게 주사용 항바이러스제인 페그인터페론 알파와 경구용 항바이러스제로 나눌 수 있으며 경구용 항바이러스제는 내성발현의 유전자 장벽에 따라 크게 두 부류로 나뉜다. 엔테카비어, 테노포비어DF, 테노포비어AF, 베시포비어는 유전자 장벽이 높아 HBeAg 양성 및 음성 만성 B형간염 환자의 1차 치료약제로 권고된다. 특히 엔테카비어와 테노포비어DF는 효과와 장기간의 안전성이 검증되었으나 테노포비어AF와 베시포비어는 장기 추적 데이터가 조금 더 필요하다.

5) 경구용 항바이러스제 사용 중 치료 반응의 정의 (Table 1)

Table 1. Definition of response to nucleos(t)ide analogues therapy for chronic hepatitis B[5]

Category of response	
Virologic response	Decrease in serum HBV DNA to an undetectable level on real-time PCR assay
Partial virological response	Decrease in serum HBV DNA of more than 2 $\log_{10}$ IU/mL but detectable HBV DNA on real-time PCR assay after at least 12 months of therapy with high-potency NAs, or after at least 6 months of therapy with low-potency NAs in compliant patients.
Virologiccal breakthrough	Increase in serum HBV DNA of more than 1 $\log_{10}$ IU/mL compared to the lowest value, or redetection of serum HBV DNA at levels 10-fold the lower detection limit after achieving a virological response.
Serological response (HBeAg)	HBeAg loss or HBeAg seroconversion
Serological response (HBsAg)	HBsAg loss or HBsAg seroconversion
Biochemical response	Normalization of ALT level
Biochemical breakthrough	Increase in serum ALT level after ALT normalization on antiviral therapy
Genotypic resistance	Detection of HBV mutations known to confer antiviral resistance during antiviral therapy
Phenotypic resistance	Decreased susceptibility (*in vitro* testing) to inhibition by antiviral drugs associated with genotypic resistance
Cross resistance	HBV mutation selected by one antiviral agent that also confers resistance to other antiviral agents

6) 경구용 항바이러스제 치료 중 모니터링

경구용 항바이러스제 치료 중에는 간기능검사 및 혈청 HBV DNA를 1-6개월 간격으로 검사하고 HBeAg/anti-HBe는 3-6개월 간격으로 검사할 수 있다. 또한 치료 중에 반응 예측과 종료 시점 결정에 도움을 줄 수 있는 HBsAg 정량검사를 고려할 수 있다. 바이러스 반응이 확인된 후에도 혈청 HBV DNA를 3-6개월 간격으로 지속적으로 측정하며 항바이러스 치료시 각각의 약물 부작용에 대한 모니터링이 필요하다.

2. 만성 C형간염

1) 서론

C형간염바이러스는 전 세계적으로 3% 의 인구가 C형간염 바이러스에 감염되어 있는 것으로 추산되며 우리나라에서 만성 간질환의 15-20% 원인을 차지하여 급, 만성간염, 간경변증 및 간세포암종의 주요 원인 중 하나이다[7]. 최근 수년간 C형간염의 치료방향은 종전에 사용하던 주사제인 인터페론 없이 경구 투여약제인 직접작용항바이러스제 (direct acting antivirals, DAA)를 각 유전자형과 과거 치료 경험에 따라 병합 투약함으로써 부작용을 최소화하고, 치료기간이 짧지만 성공률은 90% 를 상회할 정도로 매우 높아 향후 C형간염 퇴치라는 이상적인 목표에 한층 가까이 접근할 수 있을지 기대된다. 그러나 C형간염 바이러스는 오염된 혈액 또는 혈액제제의 수혈이나 장기이식, 주사용 약물남용, 불안전한 주사나 의료시술, 오염된 주사기나 바늘에 찔리는 경우, 감염자와의 성접촉 등에 의해 비경구적으로 전염되므로 완치된 환자라고 하더라도 주요 감염 경로와 예방수칙에 대해 교육해야 한다. 치료 목적, 치료 대상, 치료 약제, 치료 중 및 종료 후 모니터링에 대하여 2015년과 2017년 대한간학회 C형간염 진료 가이드라인에 근거하여 요약하였다[8,9].

2) 치료 목적과 목표

만성 C형간염의 단기 치료 목표는 치료 종료 12주 또는 24주째 혈중 HCV RNA가 검출되지 않는 상태인 지속바이러스반응(sustained virological response, SVR)에 도달하는 것이다. 이를 통한 궁극적인 치료 목표는

HCV를 박멸하여 HCV 감염으로 인한 간경변증의 합병증, 간세포암종, 간외 합병증의 발생 및 이로 인한 사망을 예방하는 것이다.

3) 치료 대상

치료 여부는 간질환의 중증도, 간외 합병증, 치료 성공 확률, 심각한 부작용 발생 가능성, 동반 질환 유부, 환자의 치료 의지 등을 고려하여 개별화해야겠으나 치료 금기가 없는 모든 C형간염 환자는 치료의 대상이며 특히 F3 이상의 진행된 섬유화를 동반한 환자와 간이식 전후의 환자는 우선적으로 치료한다.

4) 치료 약제

DAA는 C형간염 바이러스의 생활사에 직접 작용하여 항바이러스 효과를 나타내며 작용 부위에 따라 HCV nonstructural protein(NS) 3/4A 단백분해효소억제제(protease inhibitor, PI), NS5A 억제제, NS5B 중합효소억제제 등이 있다. NS3/4A PI 는 HCV 증식에 필수적인 다단백 분해과정을 차단하며 asunaprevir, grazoprevir, glecaprevir, voxilaprevir 등이 있다. NS5A 억제제는 HCV 복제 및 조립을 억제하며 daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir 등이 있다. NS5B 중합효소 억제제는 sofosbuvir와 dasabuvir가 있다. 현재까지 국내에서 승인된 DAA는 ledipasvir/sofosbuvir, sofosbuvir, daclatasvir, asunaprevir, ombitasvir/paritaprevir/ritonavir, dasabuvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir가 있다. DAA로 치료할 때 각 약제의 특성을 이해하고 간기능 및 콩팥기능 등을 고려하여 적절한 약제를 선택하며 다양한 약제와 약물상호작용을 유발할 수 있으므로 반드시 치료 전에 사용하고 있는 모든 다른 약제에 대하여 상호작용 여부를 확인해야 한다.

5) 치료 중 및 치료 종료 후 모니터링

치료 전 환자에게 치료 순응도가 SVR 도달에 중요함을 주지시키고 치료 중 약제 복용의 순응도를 정기적으로 확인하여야 하며, 치료 중 새로운 약제를 사용하게 되는 경우 약제 간 상호작용을 반드시 확인해야 한다. 치료 반응에 따른 요법을 위해 평가하는 급속 바이러스 반응(rapid virological response, RVR)은 치료 4주째 검출 한계 50 IU/mL 이하의 예민한 검사법으로 혈중 HCV RNA가 검출되지 않는 상태이며, 조기 바이러스 반응(early virological response, EVR)은 치료 12주째 혈중 HCV RNA가 치료 전 기저값에 비해 2 log 이상 감소하거나 검출 한계 50 IU/mL 이하의 예민한 검사법으로 검출되지 않는 상태로 정의한다. 치료 종료 12주 또는 24주째 예민한 검사법으로 혈중 HCV RNA가 검출되지 않는 상태를 SVR로 정의하며 최근 연구에서 치료 종료 12주째 평가한 SVR과 치료 종료 24주에 평가한 SVR의 일치율이 치료 약제와 관계없이 98%로 알려져 있다. 치료 중 소실되었던 혈중 HCV RNA 가 재출현하면 바이러스 돌파현상(breakthrough), 치료 종료 후 소실되었던 혈중 HCV RNA가 재출현하면 재발(relapse)로 정의한다. 만성 C형간염에 대한 항바이러스 치료의 효과를 평가하기 위하여 치료 종료 후 12주 또는 24주째에 HCV RNA 농도를 측정하여 SVR 도달 여부를 확인하여야 하며, SVR에 도달한 경우에도 치료 전에 진행된 간섬유화가 있으면 간세포암종 감시검진과 간경변증의 일반 합병증 관리가 필요하다. 더불어 SVR에 도달하지 못한 경우, 만성간염 및 간경변증에 준한 관리가 필요하다.

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Management of Acute Variceal Bleeding

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Acute variceal bleeding is a fatal complication in patients with liver cirrhosis. Once there is suspicion of variceal bleeding, hemodynamic stabilization should be achieved through appropriate fluid therapy and red blood cell concentrate transfusion. Vasoactive drugs should be started as early as possible, and prophylactic antibiotic treatment is also needed. If acute esophageal variceal bleeding is confirmed by endoscopy, endoscopic vaiceal ligation (EVL) should be performed. In case of treatment failure, balloon tamponade can be used as a temporary "bridge" until definitive treatment can be performed. Transjugular intrahepatic portosystemic shunt (TIPS) should be considered as a rescue therapy. If acute gastric variceal bleeding is confirmed by endoscopy, endoscopic variceal obturation (EVO) or EVL should be performed in gastroesophageal varices (GOV) type 1, and EVO should be performed in the fundal varices. In case of treatment failure, TIPS may be considered as a rescue therapy. Balloon-occluded retrograde transvenous obliteration (BRTO) or vascular plug-assisted retrograde transvenous obliteration (PARTO) may also be considered in patients with gastro-renal shunt.

서 론

간경변증의 대표적인 합병증 중 하나인 위·식도정맥류는 문맥압항진증으로 인한 우회혈관 발생이 주된 인자로 작용하며,[1] 정맥류 확인을 위해 내시경 검사를 시행한 간경변증 환자의 52% 정도에서 정맥류가 관찰된다고 알려져 있다.[2] 또한 정맥류가 동반된 간경변증 환자의 약 12%에서 1년 내 정맥류 출혈이 발생하며, 출혈의 주된 위험인자로는 큰 정맥류, 정맥류에 적색징후 동반 및 비대상성 간경변증이 있는 경우이다.[3] 위·식도정맥류 출혈은 단시간에 대량 실혈을 초래하여 사망에 이를 수 있는 응급 질환으로 간경변증 환자들의 중요한 사망원인 중 하나이다.[4] 따라서 정맥류가 동반된 간경변증 환자에서는 정맥류 출혈 예방을 위한 적절한 예방적 치료가 필요하며, 급성 출혈이 발생한 경우 신속한 환자의 소생 및 안정화와 함께 빠른 시간 안에 지혈이 이루어져야 한다. 본고에서는 급성 정맥류 출혈의 응급 대처 및 치료에 대해서 살펴보고자 한다.

본 론

1. 급성 위·식도정맥류 출혈의 진단

문맥압 항진증이 동반된 환자에서 상부위장관 출혈이 있는 경우 위·식도정맥류 출혈을 의심할 수 있으며, 확실한 진단은 내시경 검사로 한다. 내시경에서 정맥류로부터 활동성 출혈이 관찰되거나 정맥류 표면에 혈괴

(blood clot)나 백태(white nipple)가 붙어있는 경우 또는 위내 혈액이 관찰되나 정맥류 이외 다른 잠재적인 출혈 병소가 발견되지 않으면 급성 정맥류 출혈로 진단할 수 있다.[5]

2. 급성 위·식도정맥류 출혈의 일반적 치료

급성 위·식도정맥류 출혈은 집중치료를 요하는 내과적 응급질환으로서 초기 순환 및 호흡 유지가 매우 중요하다. 혈역학적 안정상태를 유지하기 위해 환자의 연령, 심혈관계 질환 유무, 활동성 출혈 여부, 혈역학적 상태를 고려하여 적절한 수액요법 및 농축 적혈구 수혈이 필요하다. 이때, 과량의 수액 투여 및 수혈은 문맥압을 상승시켜 오히려 정맥류 출혈을 조장할 수 있으므로 주의가 요구된다. 일반적으로 초기 헤모글로빈 7 g/dL 미만시에 7–9 g/dL를 유지하는 제한적 수혈이 권장된다.[6] 신선동결혈장 수혈 또는 재조합 응고인자 VIIa 투여를 통한 출혈경향성의 교정 효과는 뚜렷하지 않아 권고되지 않으며,[7,8] 심한 혈소판 감소증을 보이는 환자에서는 혈소판 수혈을 고려해볼 수 있으나 아직 이에 대한 임상연구는 많지 않다.

3. 급성 위·식도정맥류 출혈의 약물 치료

위장관 출혈이 있는 간경변증 환자에서는 세균 감염의 발생 위험이 높으므로 내원 당시부터 예방적 항생제 치료가 필요하다.[9] Vasopressin, terlipressin, somatostatin, octreotide와 같은 혈관수축제는 문맥압을 감소시킴으로써 급성 식도 정맥류 출혈 환자에서 지혈 효과를 나타내므로 정맥류 출혈이 의심되는 환자에서는 가능한 빠른 시간 내에 혈관수축제 투여가 필요하다.10 위정맥류 출혈 환자만을 대상으로 한 혈관수축제 사용의 효과에 대한 임상연구는 제한적이나 위정맥류 출혈 환자가 일부 포함된 정맥류 출혈 연구들을 종합해 보면 혈관수축제는 대조군에 비해 지혈 효과를 유의하게 향상시켰다.[10-12]

4. 급성 위·식도정맥류 출혈의 내시경 치료 및 방사선 중재술

1) 급성 식도정맥류 출혈의 내시경 치료 및 방사선 중재술

내시경에서 급성 식도정맥류 출혈이 확인되면 내시경적 지혈술을 시행하여야 하는데, 내시경 정맥류 결찰술(endoscopic variceal ligation, EVL) 이 1차 치료로 권장되며 내시경 주사 경화요법(endoscopic injection sclerotherapy, EIS)은 시술 실패, 사망, 부작용 발생 위험이 높아 더 이상 추천되지 않는다.[13-17] 내시경에서 정맥류로부터 활동성 출혈이 관찰되거나 최근 출혈 흔적인 정맥류 표면에 혈괴나 백태가 확인되면 이에 대한 EVL을 시행하여야 하는데, 결찰할 부위를 후드에 정면으로 포착한 후 내시경으로 충분히 흡인하여 정맥류를 후드내로 빨아들인 후 “red out sign”이 나타나면 정맥류 기저부를 결찰해야 한다. 이후 비선택적 베타차단제 투여와 함께 남아있는 식도 정맥류에 대하여 정맥류가 완전히 소실될 때까지 2-8주 간격으로 반복적으로 EVL을 시행하는 것이 재출혈 예방에 도움이 된다. 무작위 배정 임상연구들에서 재출혈의 위험이 높은 선별된 일부 환자에서 내시경적 지혈술에 이어 조기에 경경정맥 간내문맥전신 단락술(transjugular intrahepatic portosystemic shunt, TIPS)을 하였을 때 지혈 실패율과 사망률이 감소함을 보고하였으며,[18,19] 최근 급성 정맥류 출혈 환자를 대상으로 시행된 무작위 배정 임상연구에서 내시경적 지혈분말 도포의 치료적 가능성을 제시하였는데 추가적 연구가 필요하다.[20]

2) 급성 식도정맥류 출혈의 내시경 치료 실패 후 구조요법

약물 및 내시경 치료에도 불구하고 지혈에 실패한 급성 식도정맥류 출혈 환자에서 구조요법으로서 TIPS를 우선적으로 고려해야 한다. 풍선 탐폰삽입법(balloon tamponade)은 TIPS 등의 치료 전 가교치료(bridging therapy)로서 시행할 수 있는데 약 80 - 90%의 환자에서 지혈에 효과적이기는 하나 감압 이후 재출혈 발생 위험이 50%에 이르는 것으로 보고되며,[21,22] 식도 궤양, 식도 파열, 흡인성 폐렴 등의 심각한 합병증을 유발할 수 있으므로 풍선 탐폰을 유지하는 기간이 24시간을 넘지않도록 주의가 필요하다.[23]

3) 급성 위정맥류 출혈의 내시경 치료 및 방사선 중재술

① GOV1 출혈의 내시경 치료

위식도 정맥류(gastroesophageal varices, GOV)는 식도정맥류가 위의 소만을 따라 확장된 경우(GOV type1, GOV1)와 위바닥(fundus)으로 확장된 경우(GOV type 2, GOV2)로 나뉘는데, GOV1은 좌위정맥(left gastric vein)으로부터 유입되는 혈류에 의해 형성되며 식도정맥류와 해부학적, 병태생리학적으로 비슷하기 때문에, GOV1 에 대한 출혈은 식도정맥류출혈과 유사하게 치료할 수 있다고 알려져 있다.[24,25] GOV1 출혈에 대해서 EVL 또는 내시경 정맥류 폐쇄술(Endoscopic variceal obturation, EVO) 치료 방법을 사용할 수 있는데 위정맥류는 식도정맥류에 비해 더 크고 덮고 있는 점막층이 두꺼워 충분하게 밴드결찰이 어려울 수 있으며 쉽게 밴드가 풀리게 되면 재출혈의 위험성이 있으므로 유의해야 한다. GOV1 출혈에서 EVL과 EVO의 두 치료 중 어느 하나를 먼저 권고하기에는 아직 근거가 충분하지 않으며,[11,25-28] 환자 상태와 정맥류의 크기, 출혈 양상, 의료기관의 경험과 자원 등을 고려하여 적절한 치료를 선택하도록 한다.

② GOV2와 IGV1 출혈의 내시경 치료 및 방사선 중재술

식도정맥류가 위바닥으로 확장된 GOV2와 위바닥에 정맥류가 단독으로 형성된 1형 단독 위정맥류(isolated gastric varices type 1, IGV1)를 위바닥 정맥류(fundal varices)로 통칭하며, 위바닥 정맥류는 후방위정맥(posterior gastric vein)과 짧은위정맥(short gastric vein)에서 혈류가 주로 유입된다.[29,30] 위바닥 정맥류 출혈 환자에서 가장 활발하게 시행되는 내시경적 지혈 치료는 EVO 이다. EVO는 cyanoacrylate와 같은 조직접착제(tissue adhesive)를 정맥류 안으로 직접 주입하여 지혈 및 정맥류 소실을 유도하는 치료법이다. 천자 부위는 정맥류 내부의 혈류의 방향을 고려하여 결정하는데 정맥류 중앙의 돌출된 부위는 내부 압력이 집중되는 곳이므로 가급적 피하는 것이 좋다. 시술자는 천자할 정맥류의 크기와 내부 혈류 속도, 출혈 양상을 고려하여 접착제의 주입량을 결정한다. 대표적인 조직접착제인 2-N-butyl cyanoacrylate는 경화시간을 늦추기 위해 리피오돌(lipiodol)과 1:1 정도의 비율로 혼합하여 사용하며, 혼합액을 1 - 2 mL씩 반복적으로 주입하여 치료한다. 정맥류가 크고 내부의 혈류 속도가 빠르다고 판단되는 경우에는 시술자의 판단에 따라 일회 투여량을 2 mL 이상으로 증량하기도 한다. EVO 외에도 위바닥 정맥류 출혈에서 TIPS를 고려할 수 있으며, 위신장단락(gastro-renal shunt)이 동반된 경우는 풍선차단역행경정맥 폐색술(balloon-occluded retrograde transvenous obliteration, BRTO) 또는 혈관마개보조 역행 경정맥 폐색술(vascular plug-assisted retrograde transvenous obliteration, PARTO) 등의 치료 방법을 고려할 수 있는데 임상적 판단에 따라 빠르고 안전하게 적용이 가능한 치료를 선택하도록 한다.

4) 급성 위정맥류 출혈의 내시경 치료 실패 후 구조요법

내시경 치료로 급성 위정맥류 출혈의 초기 지혈에 실패하는 경우 구조요법으로 TIPS를 고려할 수 있다.[31,32] 불응성 출혈에서 비록 소규모 연구이지만 BRTO도 TIPS와 비교하여 유사한 지혈 성적을 보였기 때문에 위신장단락이 동반된 환자에서 고려해 볼 수 있다.[33, 34]

요약 및 결론

급성 정맥류 출혈은 단시간에 대량 실혈을 초래하여 사망에 이를 수 있는 응급 질환으로, 급성 정맥류 출혈이 의심되는 경우 우선적으로 적절한 수액요법 및 농축 적혈구 수혈을 통해 혈역학적 안정을 이루어야 하며, 가능한 빠른 시간 내에 혈관수축제 투여가 권장된다. 세균 감염의 발생 위험이 높으므로 예방적 항생제 치료가 함께 필요하다. 이후 내시경 검사를 통해 급성 식도 정맥류 출혈이 확인되면 EVL을 시행하고, 지혈에 실패하는 경우 풍선 탐폰삽입법을 해볼 수 있으나 유지 기간이 24시간을 넘지 않도록 하며, 구조요법으로서 TIPS를 우선적으로 고려해야 한다. 내시경 검사를 통해 급성 위정맥류 출혈이 확인되는 경우에는 GOV1에서는 EVO 또는 EVL을 시행하고, 위바닥정맥류에서는 EVO를 시행한다. 지혈에 실패하는 경우에는 구조요법으로 TIPS를 고려할 수 있고 위신장단락이 동반된 환자에서는 BRTO 또는 PARTO를 고려할 수 있다. 환자의 출혈 양상에 따라 적절한 치료 방법이 선택되어야 한다.

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Liver Transplantation: When and How?

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간이식: 언제 어떻게 하나?

김 범 수

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Liver transplantation (LT) is well-established and well-accepted therapeutic options for patients with acute and chronic liver failure and hepatocellular carcinoma. In 1963, Starzl et al. performed the first LT in a patient with biliary atresia.

In 1983, the National Institutes of Health (NIH) reported that the liver was no longer an experimental procedure and should be regarded as a therapeutic option for patients with end-stage liver disease and is worth expanding its application. In 1988, the first deceased donor LT in Korea was performed in a patient with Wilson's disease. Recently, LT has evolved rapidly the past two decades and outcomes of LT are improving due to postoperative management, operative technique development, development of immunosuppressive drugs, etc. The indications for liver transplantation has been expanded. In recent years, approximately 1300 to 1500 liver transplantation are being performed annually.

Patients are usually considered for liver transplantation if they have evidence of fulminant hepatic failure, a life-threatening systemic complication of liver disease, more commonly, cirrhosis with complications such as hepatic encephalopathy, ascites, hepatocellular carcinoma, hepatorenal syndrome, or bleeding caused by portal hypertension.

However, there has been no definite guideline when to consider and how to prepare for liver transplantation for individual patient with terminal liver disease.
Therefore, we review when to consider liver transplantation and how to prepare for liver transplantation in Korea.

Keywords: Indication, Liver transplantation

서 론

간이식은 1963년 미국의 스타즐 (Thomas E. Starzl) 교수에 의해 담도폐쇄증이 있는 소아 환아에게서 최초로 시행되었다. 이후 1983년 국립보건원에서는 간이식은 더 이상 실험적인 시술이 아니며, 말기 간질환 환자들에게 치료적인 방법으로 여겨져야 하며 그 적용을 확대할 가치가 있다고 하였다. 최근 수술 전후 관리 및 술기의 발달, 면역억제제의 개발 등으로 간이식 후 성적은 크게 향상되었으며 간이식의 적응증도 확대되고 있다. 현재 간이식의 적응증은 급성 혹은 만성 질환에 의해 간기능 부전이 악화되어 보존적 치료, 내과적 치료에도 간기능의 호전이 없는 경우로 간이식으로 치료가 가능한 경우가 그 적응증이다. 급성간부전의 원인으로 약물성 간염과 B형, C형 간염의 악화 등이 있고 대사성 간질환 등이 전격성 또는 급성 간부전을 일으킬 수 있다. 만성 간부전으로 바이러스성 간염에 의한 진행성 간경변증, 알코올성 간질환, 자가면역성 간염, 선천성 담도폐쇄증, 윌슨

씨병, Budd-Chiari증후군 등이 원인질환이며 진행하는 심한 황달, 조절되지 않는 복수, 정맥류 출혈, 조절되지 않는 간성혼수, 간에 국한된 절제할 수 없는 간세포암 등이 간이식의 적응증이 된다.[1,2] 급성간부전의 경우 내과 치료와 예상할 수 없는 병의 악화로 이식센터로 조기에 전원하는 것이 중요하다. 하지만 이식장기의 부족과 높은 이식 후 단기 사망율을 고려하여 내과적, 외과적, 정신과적인 금기사항이 있는지 이식이 적응이 되는지 신중하게 결정하여야 한다. 이식 승인을 받은 환자는 대기자 명단에서 병의 중증도에 따라서 우선순위가 부여된다. 따라서 원인 간질환과 합병증에 대해 언제, 어떻게 적절한 간이식등록 및 평가를 하는지 기술하고자 한다.

국내 간이식 현황

뇌사자 간기증의 부족으로 우리나라를 포함한 대부분의 아시아 국가에서는 뇌사자 간이식을 대신해 생체간이식이 활발하게 진행되고 있다. 2017년 KONOS 연보에 따르면 간이식 대기자는 5,295명이었며 뇌사자 간이식 450건, 생체간이식 1032건으로 총 1482건의 간이식이 시행되었다. 이식자의 평균 대기시간은 155일이었다. 주된 이식 적응증은 만성 B형간염에 의한 간경변, 간세포암, 알코올성 간질환 등이었다. 이식 후 생존율은 뇌사자에서 3개월, 1년, 3년, 5년 82.7%, 78.0%, 72.5%, and 69.6%였고, 생체간이식에서 3개월, 1년, 3년, 5년 94.1%, 89.7%, 83.3%, and 80.6% 이었다.

적절한 간이식에 대한 시기결정

적절한 간이식에 대한 시기결정은 다음의 3가지 단계에 의존한다. 첫째 이식센터로의 전원, 둘째 이식팀에 의한 신중한 평가 후 뇌사자 등록 셋째 내과적 치료 및 이식편 우선순위 및 할당에 관한 정책이다.

예측할 수 없고 빠르게 진행되는 급성 간부전 및 중증의 간염 환자는 이식센터에 의뢰를 해야 하며 간경화 환자의 경우 보통 간성혼수, 복수 간암, 간신증후군, 식도정맥류출혈 등의 합병증이 발생하며 이식센터로 의뢰된다.

뇌사자 장기의 부족으로 수혜자의 엄격한 선별기준이 적용되는데 이러한 선별기준으로 이식하지 않았을 때보다 이식했을 때 낮은 단기 사망율을 예측할 수 있고 금기증 환자를 배제할 수 있다.

간이식의 절대적인 금기증은 중증의 심폐질환, 조절되지 않은 활동성 감염이나 패혈증, 간외 악성종양, 간암의 간외 전이, 현증의 알코올 및 약물중독, 고도비만, 간이식이 불가능한 해부학적 이상, 뇌사 등이 있다.[1]

급성 간부전

급성 간부전은 잠재적으로 가역적인 간손상으로 이전에 간질환의 병력이 없는 건강한 사람에게서 간기능 손상으로 최초 증상발생 후 8주이내에 급격히 간응고 장애, 간성혼수가 진행하는 경우를 말한다. 원인으로는 약에 의한 것이 가장 많으며 바이러스성 혹인 원인 미상인 경우도 있다.[4]

이러한 환자의 10% 미만에서 간이식이 시행된다. 두개강 내 고혈압 및 수술 전후 관리가 어려워 생존율은 낮았으나 최근의 생존율은 1년 79%, 5년 72%로 보고된다.[4] 보존적 치료 혹은 간이식을 선택하는 기준은 임상의의 판단이 중요하고 객관적인 지표로 King's College 기준이 참고가 되고 있다.

간성 뇌증이 없는 환자라도 INR>1.5인 환자는 이식센터로 전원해야 하며 간성 뇌증이 나타나면 급성 간부전을 진단이 이루어진다. 이후 임상증상은 급격히 악화되며 응급 간이식을 위한 등록을 해야 한다. 간성 혼수 3, 4 단계에서는 수일 내에 패혈증 뇌부종, 심폐기능부전, 다발성 장기부전이 일어날 수 있다.

만성간질환에서의 간이식 적응증

간의 합성능력저하에 대한 정도는 CTP 점수에 잘 반영되어 있고 만성간질환 환자의 중증도를 평가하는 수단으로 잘 알려져 왔다. 그러나 CTP점수는 주관적인 평가가 반영되고 말기간질환 환자의 생존율의 예측할 수 있는 신기능이 고려되지 않는 단점이 있다. 이에 혈청 빌리루빈, 크레아티닌, INR을 기반으로 하는 새로운 객관적이 예측모델을 개발하였는데 MELD score이다. 미국에서는 2002년부터 MELD점수에 따라서 수혜자 우선순위

를 두었고 우리나라에서는 2016년 6월부터 MELD점수에 따라서 이식 편을 제공하고 있다. 만성간질환환자에서 간이식을 받지 않았을 때 보다 간이식을 받음으로써 생명연장이 가능하거나 삶의 질이 향상된다면 간이식의 적응증으로 고려해야 한다.[5]

MELD점수 [MELD risk score=10×[0.957 × logeCr (mg/dL) + 0.378 × logeBil (mg/dL) + 1.120 × logeINR + 0.643 × cause of cirrhosis (0 alcohol, cholestatic; 1 other etiology); 6~40]로 환산하여 15점 이상일 때 간이식을 권유할 수 있는데, 이는 이식 대기 중 사망에 의한 이탈률을 최소화하면서 간이식 후 생존율을 최대화하는 점수라고 하겠다.

간세포암에서의 간이식 적응증

간세포암에서 간절제술과 간이식은 근치적 치료이다. 하지만 단순히 하나의 방법으로 모든 간암환자에게 적용하기는 어려우며 잘 선택된 환자에서 간절제 및 이식은 5년 생존율 60~80%으로 최상의 결과를 얻을 수 있다.

간경화와 만성 B형간염을 동반한 모든 환자에서 일차병원에서 간암의 선별 검사를 하고 있으며 따라서 일차의료를 담당하는 의사가 간이식이 간암의 치료 방법 중 하나라는 것을 인식하여야 한다.

이태리 밀란(Milan) 그룹은 영상검사에서 간외 전이와 혈관침범이 없고, 단일결절인 경우 5 cm 이하, 다발성인 경우 결절이 3개 이하이면서 각 결절이 3 cm 이하인 간세포 암종 환자에서 간이식 후 4년 생존율 75%, 무병생존율 83%라는 우수한 성적을 발표하여 간세포 암종 환자에서의 간이식 기준을 제시하였다. 밀란 척도 내에 포함되는 간세포 암종 환자에 있어서 간이식은 가장 좋은 무병 생존율을 보장할 수 있는 매우 이상적인 치료법이다.

밀란 척도 시행 후 간암에서의 간이식은 전세계적으로 증가해왔으며 아시아에서 간이식의 적응증에서 1/3을 차지하며 미국과 유럽에서는 10~20%를 차지하고 있다. 하지만 아시아에서는 기증자의 비율이 상대적으로 낮아 이러한 간암환자들이 뇌사자 간이식을 받을 확률이 낮아 생체 간이식이 요구된다. 밀란 척도와 같이 간의 배분하는 시스템에 영향을 받지 않고 이식을 할 수 있기 때문에 많은 아시아 센터에서는 확장된 간암기준을 채택하여 사용하고 있다.

MELD 점수는 간경변의 단기성적을 예측하여 가장 위중한 환자에게 간을 제공하는 시스템이다. 하지만 종양의 이식 후 진행예측, 효과적인 이식 및 생존율을 예측하기 어렵다.

간세포암의 진행으로 인하여 대기자 명단의 탈락이 문제가 된다. 미국의 UNOS (United Network for Organ Sharing)에서는 간이식 대기 우선순위를 결정하기 위해 MELD 점수를 도입하여, 처음 등록 후 6개월이 지난 후에도 밀란 척도 범위에 있다면 MELD 점수 28점을 주고, 이식 대기 후 3개월마다 10%의 가산점을 준다. 그러나 우리나라는 국립장기이식관리센터에서 KONOS (Korean Network for Organ Sharing) 등급제를 운영하였고 간세포암종 환자에 대한 가산점이 없었다. 이러한 문제를 해결하고자 2016년 6월부터 MELD 점수를 도입하여, 간세포 암종이 밀란 척도에 해당되는 경우, 대기자의 MELD 점수가 0~13인 경우 4점을 추가, MELD 점수 14~20인 경우 5점 추가, MELD 점수 21점 이상은 추가 점수를 부여하지 않도록 개정하였다. 하지만 대부 MELD점수가 30점 이상인 경우에 시행되기 때문에 간세포 암종 환자가 상대적으로 간을 배정 받기는 어렵다.[6]

종양의 진행을 막으며 이식까지의 가교 치료로서 절제술, 고주파치료 경동맥색전술, 방사선치료 등이 시행될 수 있지만 효과에 대해서는 자료가 부족하다.[7]

지방간 환자의 간이식

비 알코올성 간질환은 단순 지방간에서 간경화에 이르기까지 다양한 임상증상을 나타내며 현재 서양인구에서 25~35% 아시아에서 5~15% 가 영향을 받고 있다.[8] 말기간질환환자는 이식을 고려해야 하며 이것은 영구적인 치료가 아니며 NAFLD가 이식 후 재발하는 것으로 나타났다.[9] 이것은 다양한 인자에 의해 영향을 받으므로 이식 전후에 체중조절 및 적절한 식이 요법과 당 및 지질 조절이 필수적이다.

자가면역성간질환

자가면역성 간질환은 자신의 간조직 내에 표현되는 항원에 대한 면역관용의 결핍으로 발생하는 질환군으로 자가면역성 간염(autoimmune hepatitis, AIH), 원발성 담즙성 간경변(primary biliary cirrhosis, PBC)과 원발성 경화성 담관염(primary sclerosing cholangitis, PSC)가 해당한다.[10]

자가면역성 간질환에서의 간이식은 다른 말기간질환에서와 마찬가지로 합병증을 동반한 간부전이 발생할 때 적응증이 된다. 즉 중증의 치료에 반응하지 않는 소양증 또는 중증 간성 뇌증 등이 발생시 이식을 고려한다.

담관 협착과 관련된 재발성 담관염 등도 드물게 간이식의 적응증이 된다. 경화성 담관염 환자에서 담관암의 발생은 10년간 7~9%로 보고되며 높은 재발율로 간이식의 금기이지만 미국 메이요 병원에서는 잘 선택된 환자에서 술 전 항암방사선 치료 후 간이식으로 좋은 성적을 보이고 있다.

알코올성 간질환에서의 간이식

알코올성 간질환은 유럽과 북미에서 가장 흔한 간이식의 적응증으로 전체 간이식의 20-30%를 차지하며 점차 증가 추세에 있다.[11,12] 전원시기 및 장기배분 등은 간경변의 일반적인 규칙에 따라 적용된다. 다른 질환과 달리 대부분의 간이식 센터에서는 6개월간의 금주를 해야만 뇌사자 등록을 하는데 첫번째 이유는 금주기간 동안 간기능이 호전되는 시간을 주며 둘째로는 이식 후 재음주 가능성을 예방하기 위해서이다. 이식환자의 재음주율은 다양한데 19-50%로 보고되고 있다.[13]재음주율의 위험성을 고려하지 않은 채 뇌사자 장기를 배분하는 것은 윤리적이 논란을 야기할 수 있다. 심한 알코올성 간염은 단기간의 사망률이 높고 부신피질 호르몬이 주된 치료이다. Lilley점수가 0.45 이상인 환자는 스테로이드에 반응하지 않는 환자로 간주되며 결과가 좋지 않으므로 6개월의 금주기간 없이 뇌사자 간이식을 구조치료로 점차 많이 하고 있는 추세이다. 그러나 장기의 부족으로 모든 환자의 심한 알코올성 간염이 임의로 간이식을 위해 선택할 수 없다. 이식편을 제공받는 환자를 선택하는 엄격한 기준 하에 심한 알코올성 간염에서의 간이식은 단기 및 장기 생존율을 높일 수 있는 치료방법이다.

결 론

간이식을 준비하기 위해 일정기간이 소요되며, 간이식의 성과를 극대화하기 위해서는 간경변증의 치료 중 하나가 간 이식임을 항상 염두해 두어야 할 것이다.

심한 간염, 급성간부전, 생명을 위협하는 간질환의 합병증이 있는 간경화 환자는 간이식센터로 전원되어 적절한 간이식 등록을 받아야 한다. 간경화의 합병증은 종종 다른 방법으로도 효과적으로 치료될 수 있지만 그러한 합병증은 간이식을 고려해야 하는 간질환의 자연경과의 변화를 의미한다. 간이식센터에서는 환자의 간질환의 중증도, 합병증 및 금기증을 잘 판단하여 간이식을 결정하여야 한다.

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Hepatocellular Carcinoma: Diagnosis and Tumor Staging

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간세포암종: 진단과 병기 평가

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서 론

우리나라 시민들의 가장 중요한 사망원인은 암으로, 두번째 원인인 심장질환보다도 유의하게 높게 평가된다. 2017년 자료에 의해 악성신생물에 의한 사망을 보면 전체 연령에서 간암에 의한 사망은 남성에서 2위, 여성에서는 4위의 원인으로 평가되었으나, 40~59세 사이에서는 간암으로 인한 사망률이 1위로 평가되었다. 지난 20여년간 연간 절대 간암 조사망률과 조발병률은 증가하였으나 연령표준화사망률과 연간표준화발병률은 감소 추세를 보이고 있는데, 이는 우리 나라 인구집단과 간암 발병자들의 연령분포가 빠르게 고령화되고 있는데 기인한 것으로 추정된다. 여전히 소폭 증가추세를 보이는 간암 조사망률과 조발병률을 극복하기 위한 수단으로 간암, 특히 간세포암종의 정확한 진단과 병기 평가는 중요하게 평가된다.

본 론

간세포암종의 고위험군으로 평가하는 만성 B형간염, 만성 C형간염, 간경변증환자에서 6개월 간격으로 간 초음파검사와 알파태아단백검사를 시행하는데, 이러한 감시검사에서 간 종괴가 확인될 경우 어떠한 성격의 병변인지 확인 해야할 필요성이 대두된다.

I. 간세포암종의 진단

1) 병리학적인 진단: 병리 검사를 통한 진단

간질환의 진단을 위한 영상학적 방법의 발달로 인하여 생검을 통한 조직학적 진단의 필요성이 많이 감소하고 있긴 하지만, 간생검은 아직도 주요한 진단의 수단이다. 간 종괴가 확인된 경우 간암의 진단이 영상학적 방법으로 가능하다면 조직학적 진단은 필요하지 않을 수 있겠지만, 영상학적 소견이 전형적이지 못 할 경우 조직학적 진단이 필요할 수 있다.

대부분의 간암환자는 그 기저에 간경변증을 동반하고 있는 경우가 많아서 실제로 간생검을 시행하기 어려운 경우가 많다. 세침흡입세포검사, 세침흡입생검, 침핵생검 등에 의한 진단 민감도는 67~93%로 다양한 점, 2 cm 이하의 소간암의 경우 그 민감도가 더 떨어질 수 있는 점, 생검을 통한 암종의 전파가 0.6~5.1% 정도로 보고되는 점, 생검 자체의 위양성률이 33% 정도로 보고되는 점 등의 이유로 대부분의 간암 진단은 임상적 기준에 따라 비침습적으로 진단된다. 대한간암학회/국립암센터에서의 진료가이드라인에 따르면 간세포암종의 고위험군에서 1 cm 이상의 결절이 확인되고 역동적 조영증강 CT, 역동적 조영증강 MRI, 또는 간세포특이조영제를 이용한

MRI중 하나 또는 둘 이상에서 간암에 합당한 소견이 없거나, 1 cm 미만의 간결절이 발견된 경우 간염 활동성이 억제된 환자에서 혈청 aFP가 정상범위보다 상승되고 추적검사에서 지속적으로 상승하며 상기 영상검사 중 둘 이상에서 합당한 소견을 보이는 조건에 해당되지 않거나 간암의 전형적인 소견을 보이지 않는 경우에 진단을 위해 간 생검을 고려하는 것으로 권고된다(Fig. 1).

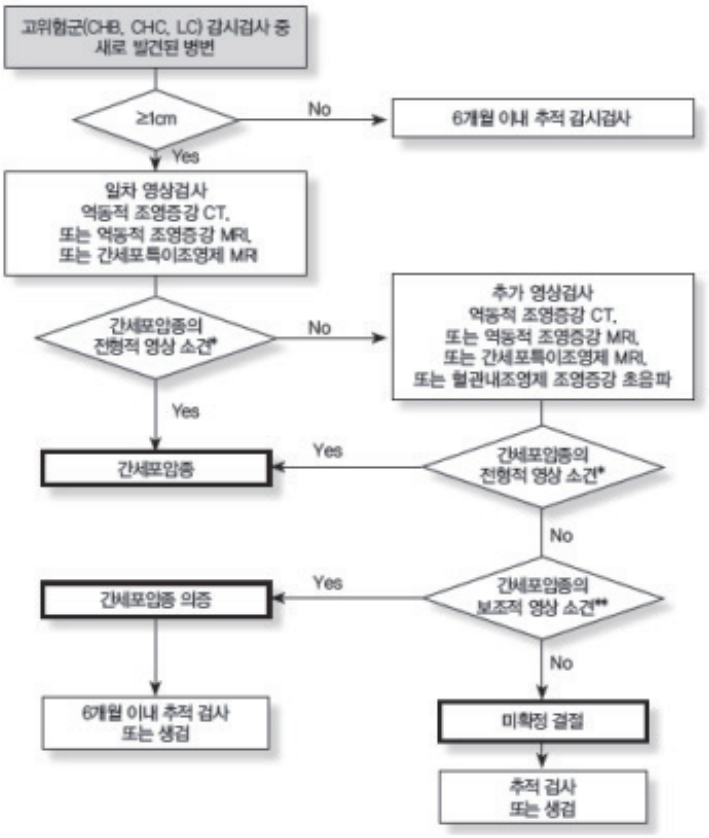


Figure 1. KLCA/NCC diagnostic algorithm and recall policy in patients with a high risk of hepatocellular carcinoma.

2018년 AASLD의 진료가이드라인에서는 1 cm이상의 간세포암종에서 동맥기 조영증강과 문맥기 조영감소의 전형적인 소견을 보이는 일반적인 진료가이드라인의 권고대로 진단 시 90% 이상의 특이도를 보이므로, 이러한 진료가이드라인에서의 기준을 만족하지 못 하거나 1 cm보다 작은 경우에는 조직검사를 고려할 수 있다고 권고한다.[1]

2) 영상학적 방법을 통한 진단

간세포암종의 고위험군에서 감시검사 중 발견된 1 cm 이상의 결절은 진단을 위해 역동적 조영증강 전산화단층촬영, 역동적 조영증강 자기공명영상 혹은 간세포특이조영제 조영증강 MRI 를 일차 영상검사로 시행하는데, 역동적 조영증강 CT의 병변별 민감도는 76%, MRI 83%, 환자별 특이도는 CT 91%, MRI 89%였고, 간세포특이조영제를 사용하였을 경우에는 세포외액조영제를 사용한 역동적 MRI보다 높은 민감도(85.6% vs. 77.5%)와 양성 예측도(94.2% vs. 83.6%)의 메타분석 결과를 보였다.[2,3] 일차 영상검사에서 전형적인 소견을 보이지 않을 경우, 단계적으로 역동적 조영증강 CT, 역동적 조영증강 MRI 혹은 간세포특이조영제 MRI, 혈관내조영제 조영증강 초음파를 통한 추가 영상검사를 시행하여 민감도를 향상시킬 수가 있다.

간세포암종의 전형적인 영상진단은 1 cm 이상의 병변이 역동적 조영증강 CT, 역동적 조영증강 MRI 혹은 간세포특이조영제 MRI에서 동맥기 조영증강과 문맥기, 지연기 혹은 간담도기에서 조영제 씻김현상을 보일 때를 의미한다. 전향적 연구에서 역동적 조영증강 CT 또는 MRI의 동맥기 조영증강 및 문맥기 또는 지연기 조영제 씻

김현상만을 진단 기준으로 하였을 때 민감도는 약 65-89%, 특이도는 91-100%로 보고된다. 간세포암종의 고위험군에서 감시검사 중 새로 발견된 1 cm 미만 결절은 6개월보다 짧은 간격으로 추적 초음파검사를 시행한다.[4]

II. 병기 평가

간세포암종의 병기는 환자의 예후를 평가하고 적절한 치료를 결정하는데 필요할 뿐 아니라 서로 다른 치료법에 대한 연구의 결과를 비교하는데 필수적으로 현재까지 다양한 병기 분류법이 개발되어 왔고, 전술한 바와 같이 대부분의 간세포암종 환자는 기저 간기능 장애를 가지고 있기 때문에 간세포암종 환자의 예후를 평가하기 위해서는 간세포암종의 요소와 원격전이 여부 뿐 아니라 간기능의 평가가 중요할 수 있다.

간세포암종의 병기 분류중 하나인 Okuda 분류법은 간세포암종의 크기 뿐만 아니라 혈중 알부민, 빌리루빈, 복수 유무 등 환자의 기저 간기능을 병기 분류에 포함시킨 최초의 분류법으로서의 의의가 있지만, 이 분류에서는 분석에 사용된 대부분의 환자가 진행된 간세포암종 환자이었기 때문에 초기 간세포암종의 경우에 사용하기에는 적절하지 않은 단점이 있다(Table 1). 이후 발표된 병기 중 환자의 간기능을 포함시킨 대표적인 것으로는 Cancer of the Liver Italian Program (CLIP) 분류, Barcelona Clinic Liver Cancer (BCLC) 분류, Japan Integrated Staging (JIS) 분류 등이 있다.

Table 1. Okuda classification

	Tumor size >50%		Ascites		Albumin (<3 g/dL)		Bilirubin (>3 mg/dL)	
Stage	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)
I	(-)		(-)		(-)		(-)	
II	1 or 2 (+)							
III	3 or 4 (+)							

CLIP 병기는 환자의 간기능과 종양의 크기, 알파태아단백, 문맥침범 유무로 병기를 결정한다. 합산된 점수에 의해 CLIP 0에 속하는 간세포암은 종괴의 크기에 대한 세부 분류가 없이 전체 간 부피의 50% 미만으로 정의하고 있어서 초기 간세포암종의 분류에 취약한 단점이 있어서 수술이 가능한 환자의 치료 후 예후 추정이 어려울 수 있다(Table 2).

Table 2. Cancer of the Liver Italian Program(CLIP) classification

Variables	Scores		
	0	1	2
Child-Pugh stage	A	B	C
Tumor morphology	uninodular and extension ≤50%	multinodular and extension ≤50%	massive or extension >50%
AFP (ng/dL)	<400	≥400	
Portal vein thrombosis	no	yes	

BCLC 분류는 환자의 간기능 평가에 있어서 Child-Pugh 등급 외에 ECOG 수행능력, portal hypertension 유무 등을 추가시킨 특징이 있는데 단순히 환자의 병기만을 분류하는 것이 아니라 각각의 병기에 해당하는 치료법을 정한 치료 지침의 성격을 또한 가지고 있다(Fig. 2). BCLC 분류법은 미국간학회 간세포암 치료 가이드라인에서도 채택되어 널리 사용 중이지만, intermediate stage의 정의가 ECOG 0로 한정되어있고, 경동맥화학색전술의 적응증을 이 환자들 만을 대상으로 한 것은 임상 현장에서 의견의 차이가 있어 intermediate와 advanced stage의 세부 분류가 더 필요할 것으로 보여진다.

JIS 분류법은 일본 간암연구회에서 정의한 TNM stage와 Child-Pugh 등급에 따라 점수화 하여 환자를 분류하는 것으로, CLIP 분류법과 비교하여 초기 간세포암 환자의 분류에 장점을 가진다 (Table 3).

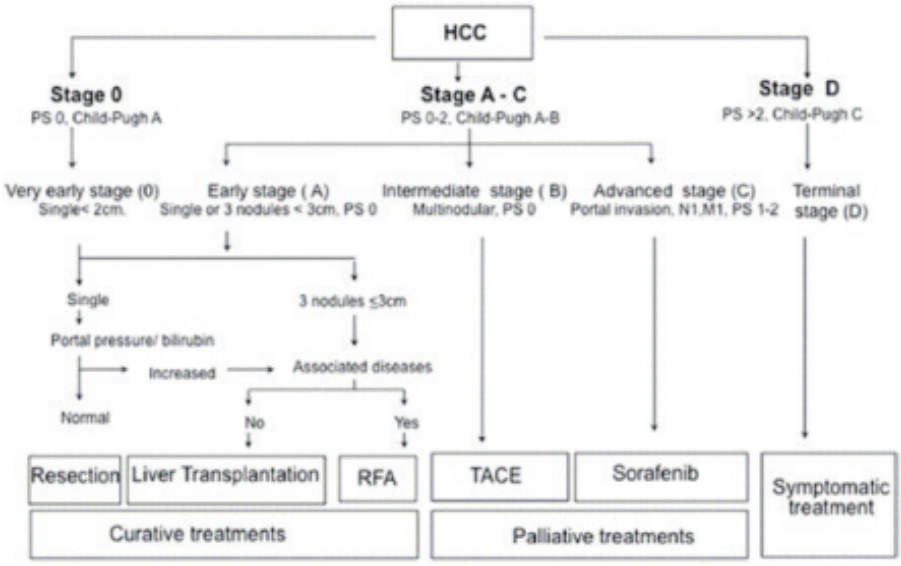


Figure 2. Barcelona Clinic Liver Cancer (BCLC) classification; M, metastasis classification; N, node classifcation; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Table 3. Japan Integrated Staging (JIS) classification

Variables	Scores			
	0	1	2	3
Child-Pugh grade	A	B	C	
TNM stage by LCSGJ	I	II	III	

위의 분류법과 다르게 전통적으로 간세포암 자체의 병기를 분류하는 것으로 American Joint Committeeon Cancer (AJCC) tumor node metastasis (TNM) 병기가 있으며, 이 분류법은 BCLC와 더불어 여러 연구에서 널리 사용되고 있는데 섬유화 정도가 포함되어 있는 특징이 있다(Table 4).

Table 4. American Joint Committee on Cancer (AJCC) TNM staging for liver tumors (8th ed., 2017)

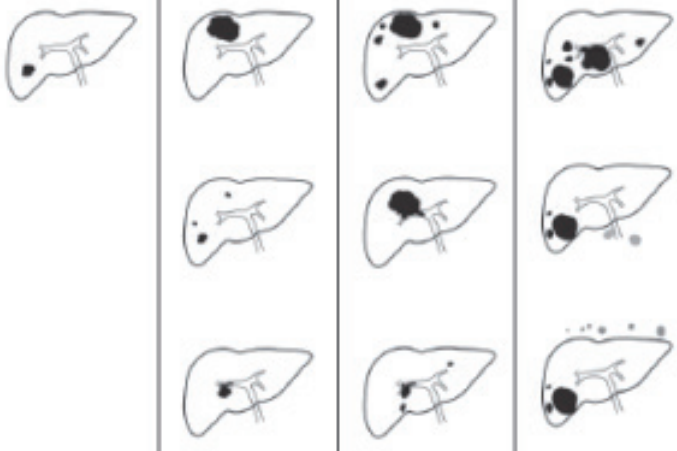
	Primary tumor (T)	Regional lymph nodes (N)		Distant metastases (M)	
T1a	Solitary tumor ≤2 cm with/without vascular invasion	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T1b	Solitary tumor >2 cm without vascular invasion	N0	No regional lymph node metastasis	M1	Distant metastasis
T2	Solitary tumor >2 cm with vascular invasion or multifocal tumors, none >5 cm	N1	Regional lymph node metastasis		
T3	Multifocal tumors at least one of which is >5 cm				
T4	Single tumor or multifocal tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum				
Stage					
Stage IA	T1a	N0	M0		
Stage IB	T1b	N0	M0		
Stage II	T2	N0	M0		
Stage IIIA	T3	N0	M0		
Stage IIIB	T4	N0	M0		
Stage IVA	Any T	N1	M0		
Stage IVB	Any T	Any N	M1		

대한간암학회/국립암센터에서의 진료가이드라인에서 간세포암종 병기는 modified UICC 병기를 기본으로 하고, BCLC 병기와 AJCC/UICC 병기를 보완적으로 사용한다(Table 5).

Table 5. Modified UICC stage

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IV A	T4	N0	M0
	T1, T2, T3, T4	N1	M0
IV B	T1, T2, T3, T4	N0, N1	M1

Criteria	T1	T2	T3	T4
(1) Number of tumors: solitary (2) Diameter of the largest tumor ≤ 2 cm (3) No vascular or bile duct invasion: Vp0, Vv0, B0	All three criteria are fulfilled	Two of the three criteria are fulfilled	One of the three criteria is fulfilled	None of the three criteria are fulfilled



결 론

빠르게 고령화되고 있는 간암 발병자들에서 소폭 증가추세를 보이는 간암 조사망률과 조발병률을 극복하기 위한 수단으로 간세포암종 환자에서의 정확한 진단과 병기 평가는 환자의 예후를 결정하는데 매우 중요하다고 평가되므로 이를 위한 좀 더 체계화된 진단과 병기 분류법은 매우 중요하다고 평가된다.

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DAY 2: Friday, June 21, 2019 (14:00-15:40)
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The Liver Week Satellite Symposium for Regeneration Medicine

Chairs:

Shuji Terai (Niigata Univ., Japan)
Soon Koo Baik (Yonsei Univ. Wonju)

Comparison of Bone Marrow-Derived Mesenchymal Stem Cells Isolated from Normal and Cirrhotic Patients

Young Woo Eom

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Background/Aims: Mesenchymal stem cells (MSCs) have been actively studied for use as regenerative medicine for various intractable diseases including cirrhosis. In particular, autologous or allogenic MSCs isolated from bone marrow (BM) and umbilical cord have been applied in clinical trials. Nevertheless, none of the autologous MSCs of the cirrhotic patient and normal MSCs have been shown to be effective in the treatment of cirrhosis. The aim of this study is to identify the BM-derived MSCs (BMSCs) suitable for the treatment of cirrhosis by comparing the characteristics of the BMSCs isolated from the BM of liver cirrhosis patient and normal BM.

Methods: Mesenchymal stem cells from liver cirrhosis patients (BpMSCs) were obtained from Pharmicell. Normal MSCs (BcMSCs) were isolated and cultured from normal BM mononuclear cells in Lonza. Potentials of proliferation and differentiation, cell surface antigen expression, immunosuppressive activity and mitochondrial activity of BMSCs were compared and analyzed.

Results: In the early passage, the population doubling time of BpMSCs was 68 hours, 10 hours shorter than that of BcMSCs, when the BMSCs were cultured until 150 hours of population doubling time. But the number of cells finally obtained was higher in BcMSCs. Adipocyte differentiation was slightly better in BcMSCs and cell surface antigen expression (MFI) of CD90 and CD105 was higher in BcMSCs. The inhibition of active IL-1β secretion in macrophages was also higher and the activity of mitochondria was slightly higher in BcMSCs.

Conclusions: The proliferative capacity of BMSCs in the early stage of subculture was high in BpMSCs, but the differentiation potential, cell surface antigen expression, immunosuppressive activity and mitochondrial activity were higher in BcMSCs. However, there was no statistical significance. Therefore, a larger number of BMSCs need to be compared and analyzed, and there is a need to analyze the therapeutic effect in an animal model of liver cirrhosis. Therefore, it is necessary to comparatively analyze a larger number of BMSCs, and it is necessary to directly analyze the therapeutic effect in an animal model of liver cirrhosis.

Keywords: Mesenchymal stem cells, Cirrhosis, Proliferation, Differentiation, Mitochondria

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Feasibility of Enhanced PRL-1 in Placenta-derived Mesenchymal Stem Cells by Gene Modification on a Rat Model with Hepatic Failure

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Translational studies have explored the therapeutic effects of stem cells raising hopes for the treatment of numerous diseases. Liver diseases are the most common medical diagnoses worldwide and millions of people suffer from difficult-to-treat liver diseases. Currently, orthotopic liver transplantation is the only effective treatment of end-stage hepatic disease, but this procedure is associated with many problems, including the donor scarcity, operative damage, high cost, risk of immune rejection and the lifelong immunosuppressive treatments. Human placenta-derived stem cells (PDSCs) have recently been classified and have become the focus of attention in stem cell research because they are the first of the adult stem cells to appear, they have great potential for proliferation, differentiation and self-renewal, they are readily available and they are easily procured without invasive procedures. Also, PDSCs have strong immunologic privileges. Nevertheless, powerful MSCs generation through gene regulation by non-viral gene delivery system should be enhanced the therapeutic effect in degenerative medicine. In this section, we introduce enhanced PRL-1 which plays a critical role during liver regeneration in PD-MSCs (PRL-1+) using gene delivery systems, highlight the characterization of placenta stem cells and their therapeutic effects on hepatic diseases models. Also, we will discuss recent investigations that their therapeutic potential in repair of injured liver with a view to its utility in regenerative medicine.

Keywords: Hepatic cirrhosis, Liver regeneration, Phosphatase of regenerating liver-1, Placenta-derived mesenchymal stem cells

Vascularized Liver Tissue with Different Types of Endothelial Cells and Recovery Aids for Acute Liver Failure

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Aims: Liver is one of the most highly vascularized organs, so it is inevitable to make vascularized liver tissues (VLT) for implementing the nature of liver structures, physiologies and functions. We designed VLT models to produce functional and highly vascularized liver tissues and assessed the effects of each model in in vitro and in vivo.

Methods: We used simple methods that use collagen gel to induce angiogenic sprouting of endothelial cells and made VLT models with different types of endothelial cells. We assessed the morphological and functional features of each VLT model in vitro, and conducted partial hepatectomy and subcutaneous implantation to immunodeficient mice. We also observed and compared the recovery process of different VLT-implant groups.

Results: Macro-vascular endothelial cell types showed vigorous vascularization while the liver sinusoidal endothelial cell (SEC) is less effective for making vascular networks around the in vitro cultured tissues. In terms of morphological and functional advances, however, SEC cocultured VLT showed most synergic effects with hepatocytes to make in vivo like features and enhanced functionality. We designed in vivo experiments to show the possibility of VLTs to be used as bioartificial recovery aids for acute liver failure. The VLT implanted groups successfully showed much faster recovery process than the non-VLT implanted group.

Conclusion: We fabricated vascularized liver tissue models for producing functional and highly vascularized liver tissues. With these models, the liver functions were supported by the implants after the induced hepatic failure and the recovery process via regeneration of the liver was expedited.

MicroRNA Profile Analysis in Liver Fibrotic Tissue and Hepatic Differentiated Human Bone Marrow-Derived Mesenchymal Stem Cells

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Background: Although the therapeutic mechanisms of bone marrow-derived mesenchymal stem cells (BM-MSC) are still unclear, BM-MSCs play key therapeutic roles in liver fibrosis. Furthermore, microRNAs (miRNAs) are regulators in hepatic differentiation and liver fibrosis. miR-101-3p, miR-26a-5p, and miR-26b-5p are upregulated during hepatic trans-differentiation, whereas these miRNAs are downregulated in a stage of liver fibrosis. The purpose of this study is to investigate three miRNAs' roles in the hepatic differentiation of human BM-MSC (hBM-MSCs) and in hepatic stellate cell (HSC) activation.

Methods: To detect the miRNAs of hBM-MSC into functional hepatocytes and liver fibrotic tissue, the next-generation sequencing (NGS) was performed in hBM-MSCs before and after differentiation, hepatocyte, normal liver tissue, portal fibrotic tissue, and septal fibrotic tissue. To determine the effects these miRNAs, hBM-MSC was treated with mimic or inhibitor during the hepatic differentiation. HSC LX2 was treated with TGF-β1 (2.5 ng/㎖), and with or without three miRNAs mimics or inhibitor. The role of miRNA was identified through the change of liver-specific genes, EMT markers, apoptosis genes, and fibrosis genes using the quantitative real-time PCR (qRT-PCR) and western blotting.

Results: As a result of NGS analysis, three miRNAs showed a significantly higher expression level in differentiated hepatocyte-like cells and hepatocyte than hBM-MSC but lower expression level in liver fibrosis than the normal liver. At the validation phase, qRT-PCR results showed that the level of three miRNAs was up-regulated during hepatic differentiation of hBM-MSCs. In contrast, three miRNAs expression was down-regulated in TGF-β1 activated human HSC line (LX-2) and bile duct ligated (BDL) rats. Furthermore, three miRNAs were increased in BDL rats one week after transplanting BM-derived hepatocyte-like cells.
As a result of the ability of the three miRNAs to differentiate into hepatocytes, miR-101-3p and miR-26b-5p mimic promoted the hepatic differentiation of hBM-MSC. After transfection of miRNA-26b-5p and miR-101-3p, expression of hepatocyte-specific genes SOX17, ALB, HNF4α, and TAT increased on day 7. Overexpression of the three miRNA combinations resulted in more efficient induction of hBM-MSC differentiation into functionally mature hepatocytes.
However, only the up-regulation of miR-101-3p inhibited activation of LX-2 by TGF-β1. miR-101-3p caused the mesenchymal markers (SNAI1 and CDH2) and fibrosis markers (α-SMA and COL1α1) decreased in LX2. These results show that miR-101-3p have the capability to directly convert the hepatic differentiation of hBM-MSC and inhibited the TGF-β1 mediated LX2 activation.

Conclusions: In this study, we identified novel miRNAs (miR-101-3p, miR-26a-5p, and miR-26b-5p) that can regulate the hepatic differentiation of hBM-MSC and the hepatic fibrosis. Our results demonstrate that miR-101-3p may be a biomarker, monitoring the response to therapeutic effect by BM-MSC in liver fibrosis.

Keywords: Human bone marrow-derived mesenchymal stem cells (hBM-MSCs), Hepatic differentiation, Next-generation sequencing (NGS), microRNAs (miRNAs), Fibrosis

Proteomics Approach for Translational Research, Focusing on Liver Disease

Kyunggon Kim

Asan Medical Center, University of Ulsan, Korea

간질환 중심으로 본 중개연구에서의 단백체학의 응용

김 경 곤

울산대학교 의과대학 서울아산병원

High resolution mass-spectrometry coupled with effective protein/peptide separation technique have been applied on biology and translational area. And combination of other omics technology such as transcriptomics and genomics with proteomics have been extended the spectrum of its application to the precision medicine. This divergence phase of proteomics technology is playing an important and novel role as a name of proteo-genomics. At the same time, area of proteomics is reached to deep down of clinical unmet needs by not only instrument development but also deep understanding about the usefulness of proteomics application on translational research. Nowadays, proteomics also has been in convergence phase in clinical and translational area, especially in biomarker development and validation.

Herein, I would like to introduce some applications of proteomics on translational research. Especially, comparative proteome analysis for human primary hepatocytes (hPH) and liver tissues from donor in living donor liver transplantation could give us information for organ transplantation efficiacy. Also, longitudinal plasma exosome proteome analysis of mesenchymal stem cell-grafted mouse which have liver fibrosis revealed that exosome proteome can be a valuable resource of translational research.

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The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 2: Friday, June 21, 2019 (08:30-09:30)
ROOM A [2F] 201-202

KLTS Symposium 1

Conundrum: Transplanted Liver Pathology

Chairs:
Shin Hwang (Univ. of Ulsan)
Haeryoung Kim (Seoul National Univ.)

Liver Allograft Pathology: Developments in Antibody-Mediated Rejection

Christopher Bellamy

University of Edinburgh, Scotland

Antibody-mediated rejection (AMR) in ABO-compatible liver allografts is increasingly recognised as an unusual sometimes severe early complication but more prevalent later complication after transplantation, with consequences for allograft dysfunction and chronic rejection.

This presentation will begin with a brief review of functional liver microanatomy relevant to the better understanding of the pathogenesis and manifestations of antibody-mediated rejection in the liver. We will outline a credible sequence of pathologic events and emphasize the common features of antibody-mediated rejection across different solid organ allografts, which facilitate understanding and interpretation of liver allograft changes. We will then will consider in detail the microscopic features in allograft biopsies that suggest the diagnosis. The emphasis will be on practical interpretation and integration of findings, including immunohistochemistry for Complement fragment C4d deposition in the microvasculature. Specifically, we will review the recent Banff 2016 Working group criteria for the pathologic diagnosis of active AMR and illustrate examples of microvascular endothelial injury, luminal microvasculitis, arteritis and C4d deposition. We will briefly consider emerging evidence for non-HLA anti-donor antibody injury. Finally, we will review the current Banff working formulation criteria for suggesting chronic AMR-related injury in liver allograft biopsies.

Is a Protocol Biopsy Needed in a Liver Recipient?

Suk Kyun Hong

Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 2: Friday, June 21, 2019 (11:10-12:10)
ROOM A [2F] 201-202

KAHBPS-KLTS Joint Symposium

Diagnosis and Management of Combined Hepatocellular Carcinoma (HCC) and Cholangiocellular Carcinoma (CCC)

Chairs:

Hee Chul Yu (Chonbuk National Univ.)
Young Kyoung You (The Catholic Univ. of Korea)

Pathological Point of View of Combined HCC and CCA: What Is the Origin and Diagnostic Criteria of Combined HCC and CCA?

Young Nyun Park

Department of Pathology and BK21 PLUS for Medical Science Yonsei University College of Medicine, Seoul, Korea

박 영 년

연세의대 병리학교실 및 BK21 PLUS 의과학사업단

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a malignant primary liver carcinoma (PLC) defined by the unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor. This tumor, although described over 100 years ago, has attracted greater attention recently because of greater frequency and clinical recognition. The classification of combined HCC-CCA has been updated in 5th ed of WHO classification of the digestive system. In cHCC-CCA, the tumor areas with hepatocytic differentiation show the architectural and cytological features of HCC and the tumor areas with cholangiocytic differentiation show those of CCA. There is no definite data at present to support inclusion of minimum cutoff criteria of each component for the diagnosis of cHCC-CCA and this diagnosis can be made regardless of the percentage of each component, provide that they are unequivocal. Small uniform tumoral cells, with high N/C ratio and scant cytoplasm, so-called 'cancer stem cells' can be identified in various proportions either in the transitional zone between HCC and CCA or at the periphery of HCC area. Their presence and percentage is recommended to be mentioned in the pathologic report, although it does not reflect the origin of the PLC. Hence, the use of the category of cHCC-CCA subtype with stem cell features is no longer recommended. Intermediate (hepatobiliary) cell carcinoma, a histological variant of cHCC-CCA shows morphologic features that are intermediate between hepatocytes and cholangiocytes only at the cellular level without tumor area of HCC or CCA. The designation of intermediate cell carcinoma should be reserved for PLC in which intermediate features are present in the entire tumor. Cholangiolocarcinoma (cholangiolocellular carcinoma, CLC) can be a component of cHCC-CCA when a HCC or intermediate carcinoma component is present. However, if CLC is present alone, or if CLC is mixed with a CCA, it belongs to the histopathological spectrum of CCA based on its molecular characteristics.

Keywords: Combined hepatocellular-cholangiocarcinoma, Hepatocellular carcinoma, Cholangiocarcinoma

Imaging Features of Combined HCC and CCC: What Is the Difference Compared with HCC or CCC?

Chang-Hee Lee

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Combined Hepatocellular Cholangiocarcinoma (CHC) is an uncommon primary liver cancer, which comprises a mixture of hepatocellular carcinoma (HCC), cholangiocarcinoma (CCC), and/or hepatic progenitor/stem cell features.[1,2] The 2010 WHO classification system categorized CHC into classic type and subtypes with stem cell features. The CHC predominantly occur in patients with liver cirrhosis or chronic viral hepatitis, while CHC were rarely associated with biliary disease. However, CHC can have overlapping imaging features with HCC and CCC.[3]

The imaging features of CHC were diverse, ranging from HCC like wash in and wash out patterns to CCC like peripheral rim enhancement on the arterial phase and progressive centripetal enhancement pattern.[1-3] Even though the imaging feature of CHC was confused, the knowledge of typical HCC feature or CCC feature can guide the helpful guidance of the differentiation. In this lecture, I will introduce the common imaging features of the HCC compared with CHC and CCC. These are arterial globular hyperenhancement, washout, delayed enhancing capsule, paradoxical uptake of EOB on hepatobiliary phase (HBP), intra-tumoral fat, intra-tumoral hemorrhage, T2 bright signal intensity spots, and intra-tumoral septum. The CHC favoring imaging features will be also illustrated in this lecture. These CHC/CCC features are targetoid features, which visualized as peripheral rim arterial enhancement, peripheral wash out, progressive central enhancement, targetoid diffusion restriction, target sign (EOB Cloud) on HBP / transitional phase, peritumoral bile duct dilatation, and surface retraction.

To standardize the imaging diagnosis of HCC in at risk patients, the Liver Imaging Reporting and Data System (LI-RADS) was developed in 2011 and updated in 2014, 2017, and 2018. LI-RADS 2018 was also incorporated into the AASDL guideline last year. With LI-RADS, each hepatic observation is categorized according to its likelihood of benignity and HCC (LR-1 to LR-5), as well as non-HCC malignancies (LR-M). The LR-5 category allows for a highly specific diagnosis of HCC and the LR-M category includes non-HCC malignancy and HCCs with atypical imaging features.[4] To avoid the confusion from various terminology of imaging features, I will introduce the imaging illustrations of LR-M features, which are nearly similar to targetoid CHC features.

Liver MRI findings of CHC are diverse, reflecting the heterogeneous histologic features of these tumors, and their enhancement patterns reflect the tumor composition. The targetoid appearance (LR-M) was very sensitive imaging feature to identify the CHC from the HCC. And the presence of washout, intralesional fat, and intralesional hemorrhage help differentiate CHC from CCC.[1,4]

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Surgical Treatment and Prognosis of Combined HCC and CCC

Ryusei Matsuyama, Yasuhiro Yabushita, Yuki Homma, Tkafumi Kumamoto, Itaru Endo

Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Combined hepatocellular and cholangiocarcinoma (CHC) is a rare type of primary liver cancer. Allen and Lisa described the distinct pathologic characteristics of CHC in 1949, such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) coexisting in the same tumor or in the same liver. CHC was defined as a tumor containing unequivocal, intimately mixed elements of both HCC and ICC according to the World Health Organization (WHO) classification and the General Rules for the Clinical and Pathological Study of Primary Liver Cancer of the Liver Cancer Study Group of Japan (LCSGJ). The clinicopathologic features and outcomes after surgery of CHC have been reported previously. Many studies reported that CHC patients showed more lymph nodes or peritoneal recurrence than HCC, postoperative survival was significantly poorer in CHC patients than HCC patients, and poor but statistically similar to that of ICC patients. Therefore, clinical backgrounds of CHC patients were thought to be similar to those of HCC, but postoperative survival rate and type of recurrence were similar to those of ICC patients. April 1992 and December 2018, our department surgically treated 6 cases of CHC. In this study, we reviewed the some literatures about the surgical treatments and results of CHC, and the features of surgically treated CHC patients (n=6) in our department were retrospectively investigated and compared to those of patients with HCC (n=736) and ICC (n=143), and considered the treatment strategies of CHC from the view point of surgical treatment result of ICC.

Issues of Combined HCC and CCC in Liver Transplantation

Young Seok Han

Liver Transplantation and Hepatobiliary Pancreas Surgery, Kyungpook National University, School of Medicine, Kyungpook National University Hospital, Korea

Combined hepatocellular carcinoma and cholangiocellular carcinoma (cHCC-CCC) is rare, accounting for 1.0% to 14.2% of all primary hepatic malignancies. The CCC element of cHCC-CCC may represent a partial modification of the HCC, and it has been suggested that cHCC-CCC is actually a modified form of HCC involving metaplasia of the bile duct epithelium, rather than an intermediate between HCC and CCC. Compared with typical HCC, the clinicopathologic characteristics of cHCC-CCC include more frequent multifocal lesions and reduced capsule formation compared with other tumors, as well as more frequent microvascular emboli, portal or hepatic vein invasion, and lymph node metastasis. These findings suggest that patients with cHCC-CCC have a relatively poor prognosis because all of these factors are associated with higher recurrence rates. But, analyses of data from curative surgical resections have suggested that cHCC-CCC shows a better prognosis than CCC but worse than HCC.

Differential diagnosis of HCC and cHCC-CCC is often difficult and the definite diagnosis of cHCC-CCC requires histopathologic tissue confirmation. Therefore, none had been diagnosed as cHCC-CCC before transplantation by most reports.

In cHCC-CCC patients with liver transplantation, the 5-year survival was better than liver transplantation for intrahepatic CCC but poorer than that of HCC meeting the Milan criteria. Patients with tumors measuring less than 2~5 cm have good outcomes, whereas, if they have multiple and bigger tumors, they are at higher risk of recurrence, with a consequent reduction of survival.

Retrospectively collected data in literature, although without statistical significance because of very small series, seem to suggest the use of mTOR inhibitors in those kinds of patients. Exploiting the anti-proliferative and anti-angiogenetic effect of the mTOR inhibitors is the rationale that can explain why they could improve the outcome of those patients. To elucidate the effects of mTOR inhibitor, the design more studies advocating analysis of biological effects are necessary.

If summary, the role of liver transplantation for cHCC-CCC is not clear. Thus, cHCC-CCC can be prudently considered for LT indication.

DAY 2: Friday, June 21, 2019 (13:30-14:00)
ROOM A [2F] 201-202

KLTS Special Lecture

Chair:
Kyung-Suk Suh (Seoul National Univ.)

Donation after Circulatory Death Liver Procurement in Real Practice

Koji Hashimoto

Department of General Surgery, Digestive Disease & Surgery Institute, Cleveland Clinic, OH, USA

Donation after circulatory death (DCD) donors are an increasing source of transplant organs. In liver transplantation, the use of DCD donors has been well recognized as an alternative to donation after brain death (DBD) donors. However, liver transplantation using DCD donors is characterized by inferior graft survival compared with transplantation from DBD donors because of graft tissue damage from mandatory donor warm ischemia during organ procurement. Therefore, early experience has demonstrated high rates of primary graft dysfunction/non-function and ischemic biliary complication. Although graft survival and complication rates have improved over time, there is still room for improvement. DCD organ procurement is a fight against the clock. Conventionally, DCD organs are retrieved with the super rapid technique. Although this is still the standard technique, several modifications have been implemented to improve DCD graft quality, including choice of preservation solution, use of a thrombolytic agent, systemic heparin administration, and arterial reperfusion. More recently, ex vivo machine perfusion technology has been implemented in the field of DCD transplantation. In addition to a new update of DCD liver transplantation, Cleveland Clinic experience over 15 years will be presented.

DAY 2: Friday, June 21, 2019 (14:10-15:30)
ROOM A [2F] 201-202

KLTS Symposium 2

Use of Donation after Circulatory Death to Overcome the Decrease of Brain Death Donor (*K)

Chairs:
Yang Won Nah (Univ. of Ulsan)
Myoung Soo Kim (Yonsei Univ.)

Current Status and Problems of Organ Donation in Korea

Won-Hyun Cho

Korea Organ Donation Agency

한국의 장기기증 상황과 당면한 문제점

조 원 현

한국장기조직기증원

After legislation of transplant act and establishing Korea Organ Donation Agency(KODA), deceased organ donation increased continuously until we met an unexpected obstacle two years ago. The number of deceased organ donor per million population was reached up to 11.3 in 2016 but dropped down to 9.95(liver 8.69) in 2017, however, we still performed living donor organ transplantation up to 44.3 pmp(liver 19.93) in 2017. The donated organs per deceased donor were 3.35 last year.

Current problems we have are 1) decrease in family consent rate, 2) increasing old population, and 3) decreasing the main cause of brain death such as death from head trauma by traffic accident and from cerebrovascular accident. About changing cause of brain death, we don't have much work to do but for the increasing tendency of hypoxic brain injury, we need to prepare a donation procedure from circulatory death. Increasing aged population elevate the incidence of ECD rate which ask us an experienced, good skilled management and procurement.

The rate of family consent declined by 15% from the previous year because of the negative news about donor transfer which causes public sentiment. Sometimes, donation news of social leaders increased organ donation, but lasted for one or two months. But Instead, negative news deeply affected public's heart and lasted for more than a year.

In order to raise public awareness about effect of transplantation and donation, we made every possible effort to increase the number of registrants. Over the past two decades, more than 95% of Koreans are aware of the need for organ donation, 65% are willing to donate but only 4.1% were actual donor card registrant.

Recently we have a bit of conflict with other organization in relation to the discontinuation of end of life care. Most of these patients who wish to stop the end of life care are not eligible for organ donation, but some acute injured or rapidly processed cases may be considered for organ donation. We will prepare and apply standardized guidelines for treatment decisions in two conflicting end of life care under the view of patient's will and respect of dead person's life.

One of the problems we face today is the lack of medical personnel needed to manage brain death patients. The shortening of labor time that the government is enforcing is also causing serious labor shortages in medical field.

These difficult environments and medical conditions are becoming a big obstacle to the activation of organ donation. However, we are considering the implementation of DCD in a way that the western countries have applied. And we also revising the transplantation law to enforce the first person consent authorization, and end of life care.

In order to increase the number of registrants who wish to donate organs, we intend to implement active and effective campaigns and education for the public.

What Koreans are most afraid of organ donation is body damage and corruption. But the fact that our ancestors did not make pockets in the shroud and did not want to leave anything in this world after death would be a great help for our people to encourage and understand organ donation.

Current Status of Liver Allocation System

Jae Geun Lee

Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Introduction: Organ shortage is the greatest challenge in liver transplantation (LT). Many patients have died during waiting for LT, although organ allocation policies have evolved to reduce mortality among those on waiting lists. In 2002, the Model for End-stage Liver Disease (MELD) score-based allocation system was implemented in the United States, and thereafter, other countries in Europe and Latin America adopted MELD systems. However, MELD systems represent different effects around the world and continue to evolve to meet various regional requirements. In Asia, novel surgical techniques for living donor liver transplantation (LDLT) have been devised to overcome organ shortages. However, the development of organ allocation systems has been relatively neglected. Although MELD systems have been reported to generally improve outcomes in the West, the adoption of such systems in Asia might have unintended consequences, because donation rates, medical environments, and disease entities differ from those of Western countries. The Child-Turcotte-Pugh (CTP) score-based allocation system has been used in Korea since 2000. In June 2016, Korea became the first Asian country to implement a MELD score-based allocation system. This study was undertaken to investigate the short-term impact of the implementation of MELD allocation system in Korea.

Methods: We used data from the Korean Network for Organ Sharing (KONOS) database, which contain comprehensive national data on waiting lists, organ donations, and transplantations. The study population included deceased donor liver transplantation (DDLT) between June 2014 and May 2018 in Korea. All patients were followed until death, drop-out on the waiting list, or 31 June 2018. In June of 2016, KONOS implemented the MELD score to prioritize liver allocation. Outcome data were collected from June 2014 to May 2016 (24 months prior to MELD implementation), and from June 2016 to May 2018 (24 months after MELD implementation).

Results: A total of 1805 patients underwent DDLT in Korea until study period, 888 during pre-MELD era, and 917 during post-MELD era. Comparing with pre-MELD era data, portion of alcoholic liver disease increased in the post-MELD era (33.1% vs. 39.8%, $p = 0.003$), and rate of re-transplantation also increased (7.3% vs. 11.0%). Regional distribution rate was also higher in post-MELD era than that in pre-MELD era (25.8% vs. 39.0%, $p < 0.001$). Excluding Status 1 and pediatric cases, the mean and median MELD score in post-MELD era were 36±5.4 and 40 [6-40]. In same study population, the 1-year patient survival rate was 79.8% and 76.1% in the pre- and post-MELD era. ($p = 0.039$). The 3-months patient survival rates also were 85.8% and 81.3%.

Conclusion: The MELD score-based allocation system in Korea improved the fairness of DDLT allocation by providing greater organ access to the sicker patients and by reducing regional disparities. In contrast to the previous studies, the nationwide survival rate was slightly lower in post-MELD era than in pre-MELD era. MELD score-based system appears to be a good option for organ allocation, but it is not perfect thus must be improved through continuous feedback and modifications.

Institutional Issue and Limit of Donation after Cardiac Death

Dong-Sik Kim

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Although shortage of organ in comparison to waiting list is a global issue, the situation in Korea has been getting worse especially for last several years. The rate of donation after brain death (DBD) reached its peak and, in fact, has been even decreasing recently. Considering the fact that median MELD score of recipients of liver graft from DBD donors is close to 40, development of new strategy to overcome current extreme shortage of organ is urgently required.

Besides issues related to organ allocation, expanding donor pool is a critical issue. Donation after cardiac death (DCD) is a well-established way of organ donation to increase donor pool in western countries. In Korea, DCD is permitted by law only in Maastricht category IV, which means cardiac arrest in or after the process of determination of brain death. In real clinical practice, however, not a small number of potential donors misses chance of donation due to rapid aggravation of vital signs even before the first or second determination of brain death.

In this presentation, critical issues related to execution of DCD practice under current law in Korea will be discussed including limitations and potential ways to improve in legal, cultural, and medical perspectives.

DAY 2: Friday, June 21, 2019 (16:30-17:50)
ROOM A [2F] 201-202

KASL-KLTS Joint Symposium

Hepatorenal Syndrome (HRS) (*K)

Chairs:
Jae-Won Joh (Sungkyunkwan Univ.)
Jong Young Choi (The Catholic Univ. of Korea)

HRS: Definition, Pathophysiology, and Medical Management

Yeon Seok Seo

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Introduction

Ascites is the most common complication of liver cirrhosis and portal hypertension,[1] with the incidence of approximately 60% within 10 years of diagnosis of cirrhosis.[2] The appearance of ascites represents the onset of decompensation and is associated with poor prognosis with a mortality rate of 20% per year.[2] The development of ascites is related to the splanchnic vasodilatation followed by a decrease in effective blood volume and activation of vasoconstrictor system such as renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), which induce renal sodium and water retention and fluid accumulation in the peritoneal cavity.[3,4] With progression of the disease, these hemodynamic alterations lead to hypersecretion of anti-diuretic hormone (arginine vasopressin, AVP) and development of hyponatremia, which is considered as one of the important prognostic factors in patients with liver cirrhosis.[1] Despite of these efforts to compensate hypovolemia, hypovolemia due to further splanchnic vasodilatation leads to decrease in the blood flow to the kidney, and eventually renal vasoconstriction, and development of renal dysfunction, including acute kidney injury (AKI) and hepatorenal syndrome (HRS), which are associated with poor prognosis in these patients.[5]

Definition

Renal dysfunction is usually classified to AKI, chronic kidney disease (CKD), and acute on CKD according to the acuity of presentation.[6] AKI is defined as a rise in serum creatinine (Cr) of more than 50% from baseline or an increase in Cr of at least 0.3 mg/dL in less than 48h, and CKD is defined as eGFR of less than 60 ml/min for more than 3 months. Acute on CKD is defined as the increase in serum Cr of at least 50% from baseline or the increase in Cr by at least 0.3 mg/dL in less than 48h in a cirrhotic patients with GFR below 60 ml/min for more than 3 months.[6] There was significant changes in the definition of AKI compared to the previous conventional definition of increase in serum Cr level of more than 50% to a final value of serum Cr level >1.5 mg/dL in terms of addition of absolute increase in serum Cr of ≥0.3 mg/dL and deletion of cut-off serum Cr level of 1.5 mg/dL, because minor increases in serum Cr is clinically relevant and adversely affect survival in patients with cirrhotic ascites.[7,8]

HRS is the most severe form of functional renal disorder which is not responsive to volume challenge.[9] HRS was divided into two types based on prognosis and clinical characteristics: type 1 HRS (HRS1) is the rapid onset of renal failure that occurs in patients with rapid hepatic decompensation and type 2 HRS (HRS2) is the renal impairment that progress gradually over a relatively long period of time. HRS1 is regarded as a specific form of AKI, while HRS2 is included in CKD.[6] The definition of HRS was also recently updated as no improvement in serum Cr after at least 2 days of diuretic withdrawal and volume expansion with albumin in patients with cirrhotic ascites and AKI.[9] Therefore, patients could be diagnosed as and treated for HRS1 before resolution of bacterial infection and without delay until rise in serum Cr level up to 2.5 mg/dL. Considering that rapid treatment for HRS1 with va-

soconstrictors plus albumin improves treatment response and prognosis,[10] this revision of the definitions for HRS1 would be helpful for these patients.

Prevalence & Precipitating Factors

AKI is the most common form of renal dysfunction in patients with liver cirrhosis. In patients with liver cirrhosis and renal dysfunction, 70%, 17%, and 13% of the patients had AKI, acute on CKD, and CKD, respectively.[11] In addition, AKI is a common complication in patients with liver cirrhotic ascites and it develops in 19% of these patients admitted to hospital.[12] Renal function can be improved with volume replacement in about 70% of patients with AKI, while renal dysfunction does not respond to volume challenge in the remaining 30% of these patients.[12] A previous study suggested that the incidence of HRS in patients with cirrhotic ascites at 1 and 5 years are 18% and 39%, respectively.[13]

Precipitating factors can be identified in most cases of AKI (85%).[7] Most common precipitating factors are bacterial infection, large volume paracentesis, gastrointestinal bleeding, diarrhea, and overdoses of diuretics, which are very similar with those for HRS.[7] Use of vasodilators, and renal vasoconstriction due to nonsteroidal anti-inflammatory drugs (NSAIDs) or intravenous contrast agents could also precipitate the development of AKI.[12] Similarly, precipitating factors can be identified in almost half of patients with HRS, and bacterial infection, gastrointestinal bleeding, and large volume paracentesis were the most common precipitating factors for HRS.[14]

Prognosis

The development of AKI in patients with cirrhotic ascites is associated with increase in mortality and development of complications such as variceal bleeding and spontaneous bacterial peritonitis (SBP).[15,16] In a recent study suggest that AKI in patients with liver cirrhosis is frequently progressive and independently associated with mortality in a stage-dependent fashion.[17] Although recent studies suggested that vasoconstrictors or liver transplantation can improve survival in these patients,[18] HRS still represents one of the most serious complications of liver cirrhosis.[13] Median survival of patients with HRS1 is less than 2 weeks, if untreated.[13] Median survival of patients with HRS2 is 6 months.[19]

Treatment

A previous prospective observational study suggested that AKI in patients with liver cirrhosis is frequently progressive and associated with mortality in a stage-dependent fashion.[17] Furthermore, HRS may be reversed with restoration of renal blood flow by vasoconstrictors plus IV albumin or liver transplantation.[20,21] Therefore, the early identification and treatment of its cause are very important. At first, NSAIDs and diuretics should be discontinued and, in patients with hypovolemia due to bleeding, aggressive volume expansion and prompt treatment for hemostasis should be performed.[22] If renal dysfunction does not respond to these management, patients could be treated as HRS with vasoconstrictors plus albumin.[10,23,24]

Terlipressin, an analogue of vasopressin, is the firstly recommended vasoconstrictors for HRS1 treatment. Terlipressin, by stimulating vasopressin receptors in the vascular smooth muscle cells, induce splanchnic vasoconstriction, which in turn, reduce portal blood flow and portal pressure.[25] In addition, albumin increases effective arterial volume and lead to increase in preload to the heart, cardiac output, and mean arterial pressure.[26] Terlipressin plus albumin treatment improves renal function in 40-50% of patients with HRS.[10,23,27-30] This treatment is considered effective if serum Cr is reduced at least 25% within 3 days after initiation of treatment and should be continued until serum Cr level reduce below 1.5 mg/dL. After withdrawal of treatment, HRS recurs in about 20%, however,

it usually responds well to retreatment.[9] However, survival benefit of this treatment in patients with HRS1 have not been confirmed yet.[10,23]

Conclusions

AKI is a frequent complication and associated with poor prognosis in patients with liver cirrhosis, especially in patients with cirrhotic ascites. Recently, definitions for AKI and HRS were revised to facilitate prompt diagnosis and treatment in these patients, because prompt diagnosis and rapid initiation of appropriate treatment is very important, considering poor prognosis in these patients. In patients with AKI, sufficient volume replacement with intravenous albumin as well as withdrawal of potentially nephrotoxic drugs are recommended. Patients whose renal dysfunction does not response to volume replacement could be diagnosed as HRS and treatment with vasoconstrictors and albumin should be considered.

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When to Consider Simultaneous Liver Kidney and How to Prevent Adverse Renal Outcome after Liver Transplantation

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간신 동시 이식의 적응증 및 간이식 후 신기능의 보호

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Acute kidney injury (AKI) is common in patients with liver cirrhosis, occurring in up to 23% of patients with cirrhosis, while chronic kidney disease (CKD) is present in 1% of such patients. AKI after liver transplantation is unfortunately a frequent complication with a reported incidence of 12% to 95%, and liver transplant recipients develop CKD after transplantation at higher rates than heart and lung transplant recipients, with a 5-year cumulative incidence of 22%.[1] Both pre-, post-transplant renal dysfunction have associated with morbidity and mortality after LT.

Since the adoption of MELD-based liver graft allocation in 2016, the deceased donor LT was performed in recipients with high MELD score of mean 35.9, and mean serum creatinine level was 1.95 mg/dL in Korea, which trend can translate to a higher prevalence of CKD or ESRD after LT. Therefore, effort to protect the kidney in LT recipients is more important in the MELD era.

For simultaneous liver kidney (SLK) transplantation, decision to perform SLK depends on the ability to predict recovery of renal function after LT. In LT candidates with established ESRD, criteria for SLK allocation are relatively obvious and homogeneous. Current UNOS Criteria for SLK allocation in the setting of CKD in liver patients include (i) GFR $\leq$60 ml/min for >90 days and subsequent GFR $\leq$30 ml/min or requirement for dialysis and (ii) CKD because of metabolic disease that can be corrected with a liver transplant (hyperoxaluria, atypical haemolytic uraemic syndrome, familial nonneuropathic systemic amyloidosis and methylmalonic aciduria). However, in those with varying degree of AKI, it may be difficult to confirm performing SLK because renal function can recover after LTA as to duration of AKI, need for renal replacement, degree of renal dysfunction and age of the transplant recipient. UNOS Criteria for SLK allocation in the setting of AKI in liver patients include (i) duration of AKI >6 weeks with persistent GFR $\leq$25 ml/min, (ii) dialysis dependence or (iii) a combination of both. Also, criteria included “safety Net” giving additional priority to all LT alone (LTA) recipients as well as SLK recipients who experienced immediate and permanent non-function of the transplanted kidney who are on kidney waiting list after becoming dialysis-dependent or having a GFR $\leq$20 mL/min between 60 and 365 days following liver transplantation.[2]

The predisposing factors for renal dysfunction after LT can be classified as (i) drug toxicity, (ii) other disorders related to the severity of the patient`s condition and allograft dysfunction. Calcineurin inhibitor (CNI) –induced

nephrotoxicity contribute to short- and long-term renal deterioration. Delay and reduction of CNI exposure may lessen or protect against postoperative AKI and use of mTOR inhibitor in combination with CNI reduction is another option for protecting kidney early (0-12 month) after LT. Nephrotoxic drugs such as radiocontrast, aminoglycosides, amphotericin B and NSAIDs are also well known cause of developing AKI after surgery, and should be avoided when possible.[3]

In addition, control of metabolic disease such as diabetes and hypertension is essential for preventing CKD. At the initial recognition of hypertension, lifestyle modification such as adoption of a low-sodium diet, cessation of smoking, avoidance of alcohol, and loss of weight should be emphasized to the patient. Calcium channel blockers are the preferred first-line agent in patients who do not exhibit proteinuria. Meanwhile, patients with proteinuria and hypertension should take an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers.[4] The prevalence of diabetes ranges from 31% to 38% in post-LT patients and plasma glucose control must start immediately after the transplant procedure in order to improve long-term results. The suitable goal for transplant patients with identified diabetes is a hemoglobin A1c level of less than 7%. For patients with a short disease duration, younger age and few comorbidities aside from their liver problems, an HbA1c of < 6.5% is both feasible and desirable. For patients with advanced age, multiple comorbidities, high risk of hypoglycemia and/or limited life expectancy, an HbA1c of < 8.0% is a more realistic and potentially less iatrogenic objective.[5]

In conclusion, with advances in surgical technique, anesthetic management, and immunosuppression, major obstacles to rapid deterioration of the recipients have been in overcoming and the overall survival rates at 5 years after LDLT and DDLT currently exceeds 80%, and 68%, respectively. Therefore, protecting renal dysfunction after LT remains a critical issue that affects the long-term outcomes of LT recipient and precise decision for SLK is mandatory to obtain best survival benefit.

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MELD Purgatory in HRS and Allocation Policy: When to Start Renal Replacement Therapy?

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Model for End-stage liver disease (MELD) score-based liver allocation system has been adopted since June 2016 in Korea. After adoption of MELD score, the proportion of patients with MELD score >=31 occupied three-fourths of recipient. In patients with high MELD score, the impact of serum creatinine is critical to be status 2. In patients undergoing renal replacement therapy, serum creatinine level is replaced with 4 mg/dL. There are 3 indications of pretransplant renal replacement therapy in patients with end-stage liver disease and impaired renal function. The first is hepatorenal syndrome, in which type I is often benefited from renal replacement therapy. The second is impending hepatorenal syndrome combined with pulmonary edema/pneumonia. The third is impending hepatorenal syndrome combined with hepatic encephalopathy/uremic syndrome. Two latter indications require early application of renal replacement therapy. When renal replacement therapy is applied early in time before liver transplantation, the posttransplant outcome is quite comparable with those without hepatorenal syndrome. Therefore, early timely application of renal replacement therapy is reasonably recommended when it is indicated in patients waiting for liver transplantation.

When to Start Renal Replacement Therapy for Hepatorenal Syndrome

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Hepatorenal syndrome (HRS) is a reversible and functional renal failure. It occurs in patients with acute or chronic liver disease, and hepatic failure who are characterized with portal hypertension. HRS typically presents as acute kidney injury (AKI), but also can cause chronic kidney disease. Renal replacement therapy (RRT) is usually required in severe HRS, especially when hepatic encephalopathy is combined. Refractory fluid overload, hyperkalemia, metabolic acidosis, and symptomatic uremia are conventional indications of RRT. However, RRT is often required in HRS patients who lack traditional indications. Controversy regarding clinical outcomes of early vs. late RRT is ongoing despite numerous studies focusing on this issue. The timing of RRT is usually determined based on the volume status, comorbidities, and laboratory data. The concept of renal demand and renal capacity is relatively new. If metabolic demand exceeds renal capacity, RRT should be initiated even in early stages of non-oliguric AKI. In perioperative situations (before or after liver transplantation), early RRT should be considered in patients with systemic inflammatory response syndrome, pulmonary edema, and decreased reserve of cardiopulmonary or hepatic function. The modality of RRT is usually determined based on hemodynamic stability, neurologic status, and metabolic demand. Adequate timing of RRT and factors to consider when choosing RRT modality in HRS patients will be reviewed in this session.

The Liver Week 2019

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DAY 2: Friday, June 21, 2019 (14:10-15:30)
ROOM B [2F] 203

KLTS Coordinator Session (K*)

Chairs:

Kyung-Ock Jeon (Severance Hospital)
Sunyoung Son (Gangnam Severance Hospital)

Recovery Management for Old Age Recipient

Man Ki Ju

Department of Surgery, Yonsei University Gangnam Severance Hospital, Seoul, Korea

Transplantation Counseling for an Elderly Liver Transplantation Patient

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고연령 간이식 대상자의 상담

김 형 숙

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In Korea, the standard age of senior citizens is considered to be those over 65 years of age, respectively, according to laws related to senior citizens.

The age of recipients of liver transplants is also expected to advanced age as the number of people over 65 years of age is rapidly aging to 14.3 % in 2018 and 41.0 % in 2060 in Korea.

Even though similar outcomes can be achieved 1 year after liver transplantation in patients below or over 60 years of age, most studies have shown that 5-year post-transplant survival is significantly lower in recipients older than 60–70 years of age.

According to the 2017 KONOS Annual Report, the annual survival rate of the recipient of liver transplantation from a brain dead aged 65 to 74 in the country is 67.3 %, while the annual survival rate for the recipient of a liver transplantation from a brain dead aged 75 or older is 37.8 %. In contrast, the annual survival rate of the recipient of the liver transplantation by a living donor aged 65 to 74 was 84.6 %, while that of the recipient of the liver transplantation by a living donor aged in recipients older than 75 years was 74.1 %.

In general, early mortality increases in older patients with high MELD scores (>25–28) appear to be high. In the case of a good status of pre-transplantation recipient and planned living donor transplantation, the prognosis for transplants is not likely to be bad even if they are elderly liver transplant recipients.

Advanced age is significantly associated with the risk of death due to cardiovascular events and malignancy.

Therefore, counseling for the aged transplant recipient will require careful consideration of the factors caused by aging, in addition to the liver transplant complications.

국내에는 노인 관련 법마다 노인의 기준연령은 각각이나 노인 복지법은 65세 이상을 노인으로 보고 있다. 우리나라는 2018년 65세 이상 고령자는 14.3%, 2060년에는 41.0%가 될 것으로 예상되어 급속한 고령화로 접어들고 있어 간이식 수혜자의 연령의 고령화 역시 예측된다.

과거에 비하여 60세 미만 또는 60세 이상의 간이식 수혜자의 1년 생존율은 비슷할 수 있으나 60-70세의 고령 간이식 수혜자의 5년 생존율은 유의하게 낮은 것으로 보고하였다. 2017년 KONOS 연보에 따르면 우리나라 65세에서 74세의 뇌사자에 의한 간이식 수혜자의 1년 생존율은 67.3% 를, 75세 이상의 뇌사자에 의한 간이식 수혜자의 1년 생존율은 37.8% 를 나타내고 있다.

이에 반해, 65세에서 74세의 생체 기증자에 의한 간이식 수혜자의 1년 생존율은 84.6%를, 75세 이상의 생체 기증자에 의한 간이식 수혜자의 1년 생존율은 74.1% 를 나타내고 있다.

일반적으로 MELD 점수 (>25–28)가 높은 노인 환자의 조기 사망률 증가가 높은 것으로 보이는데, 이식 전 수혜자 상태가 양호하고 계획된 생체 이식의 경우 고령의 간이식 수혜자라 해도 이식에 대한 예후를 나쁘게만 볼 필요는 없을 것으로 보인다.

고령 수혜자의 경우 심혈관 질환과 악성 종양으로 인한 사망 위험등에 대한 요인이 이식 후 사망률에 대한 요인으로 예측된다. 따라서, 고령화 이식 대상자에 대한 상담은 간이식 합병증 이외에도 고령화에 따른 요인에 대한 세심한 배려가 필요하겠다.

1.

Acute Liver Failure

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급성간부전

주 동 진

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Acute liver failure (ALF) is a rare disease but it could be life-threatening and devastating condition with up to 30-50% mortality rate, which occurs mostly in patients who do not have preexisting liver disease. The incidence of ALF is around 10 cases per million persons per year in the developed countries. Some cases may be salvaged by vigorous medical treatment together with the liver's capacity for regeneration, but orthotopic liver transplantation remains the definitive therapy for medically refractory ALF.

Conventionally, fulminant hepatic failure is defined as a severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of preexisting liver disease. But, the time gap between jaundice and hepatic encephalopathy differs according to the causes of liver failure.

Globally, hepatitis A and E infections are related to acute liver failure, with rates of mortality of more than 50% reported from the developing countries. ALF can be caused by hepatitis B infection. Particularly in Korea, acute on chronic liver failure caused by hepatitis B is not uncommon and sometimes ALF can occur in patients with reactivation of previously stable subclinical HBV infection without established chronic liver disease.

Another important cause of ALF is drug-induced liver injury. Drug-induced liver injury is responsible for approximately 50% of cases of acute liver failure in the United States. Acetaminophen is the most common hepatotoxic drug that could induce ALF in western countries. Unlike western countries, herbal medicine can be noticed the cause of ALF in many Asian countries. Other causes of ALF are hypoxia-induced liver injury, neoplastic infiltration, acute Budd–Chiari syndrome, heatstroke, mushroom ingestion, and metabolic diseases such as Wilson's disease. Rarely, pregnancy-related ALF can occur before deliver of baby, which may require early delivery of the fetus. However, in many cases, the cause of acute liver failure remains unknown, despite intensive investigation. These cases often follow a subacute presentation, and rates of survival are poor without transplantation.

Supportive therapies such as albumin dialysis units or bio-artificial livers are designed to provide a favorable milieu for regeneration by detoxifying waste molecules and providing synthetic function. These devices should bridge the patients until donor organs became available, or ideally, allow the patients to avoid liver transplantations altogether. But so far, there was no report to show survival benefit in these ALF patients. Thus, liver transplantation should be considered from the early period of ALF diagnosis.

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Patient Management after Liver Transplantation

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간이식 후 환자관리

홍 승 희

삼성서울병원 장기이식센터

간이식은 B형간염, C형간염, 알코올성간질환 그리고 간암 등과 같은 다양한 원인에 의한 만성 간 질환자나 급성간부전 환자 등에게 시행되는 수술로서 국내에서는 매해 시행되는 간이식 건수가 증가하고 있다. 이렇듯 많은 수의 간이식이 시행될 수 있는 것은 이식 후 1년, 5년, 그리고 11년 생존율이 각각 86.82%, 77.88%, 71.57% 로 높고 이식 후 삶의 질 또한 향상되기 때문일 것이다.

간이식을 성공적으로 받고 보다 건강한 삶을 유지하기 위해서는 이식 전 환자의 건강 상태도 중요하지만 이식을 성공적으로 마치기 위한 이식 전 환자 준비와 이식 후 관리 또한 매우 중요할 것이다. 이에 간이식 환자의 관리를 이식전 관리, 이식 직후 관리 그리고 퇴원 후 관리로 구분하여 알아보도록 하겠다.

이식 전 단계

- 환자가 간이식 수술을 받을지에 대한 결정을 돕기 위하여 간이식 상담이 필요하다. 간이식 상담에는 간이식 시기, 이식대기자 등록, 뇌사자 간이식 대상자 선정기준, 생체 간기증자의 법적, 의학적 적합 조건, 수술 전 KONOS 승인과 소요기간, 수술 후 입원기간, 약물복용, 이식 후 합병증 그리고 비용과 일시적인 사회활동의 중단 등에 대한 내용이 포함된다.
- 이식 전 검사를 시행한다. : CT, MRI, Doppler US 등의 검사로 간 내부 악성종양 유무를 확인하고 혈관상태를 파악한다. 아울러 간암의 경우 다른 장기로의 전이가 없는 것을 확인하기 위하여 PET CT, Chest CT 그리고 Bone Scan 검사를 시행한다. 간 이외 장기의 암여부를 확인하기 위하여 위내시경이나 대장내시경, 자궁경부암, 유방암 등의 검사도 시행한다. 수술에 위험을 초래할 수 있는 심혈관계와 폐상태에 대한 정밀검진도 시행한다.
- 간이식 후에 발생할 수 있는 주요 감염에 대해 적절한 예방대책이 필요하므로 백신을 통해 예방 가능한 질병들에 대해서는 예방접종을 하는 것이 좋다. 특히 이식 후 사망률이 높은 감염 중의 하나가 폐렴이므로 폐렴구균과 독감에 대한 예방접종을 시행 한다.

이식직후-퇴원 전 단계

- 수술직후부터 퇴원 전까지의 단계로 중환자실에서 약 1주, 이식병동에서 약 2-3주간 입원하게 되는 시기이다.
- 혈역학적으로 불안정한 시기이고 감염이나 거부반응과 같은 합병증의 위험이 높아 지속적인 심혈관 감시와 정서적 지지간호가 필요하다.
- 일부 환자에서 수술 직후 출혈, 혈관합병증(ex. Hepatic Artery Thrombosis, Portal Vein Thrombosis,

Hepatic Vein Thrombosis) 등의 이유로 재수술을 할 수도 있고 일차간이식실패로 인한 재이식을 경험할 수도 있다.
- 담도합병증은 혈관합병증에 비해 빈도가 좀더 많은 것으로 보고되고 있고 가장 흔한 것은 문합부위 담즙 누출이다.
- 퇴원 후 환자의 자가관리를 극대화하기 위하여 퇴원 전 다학제로 구성된 의료인의 집단교육을 시행한다. 집단교육에 포함되는 내용으로는 사회복지사의 사회복지정보, 영양사의 영양관리, 약사의 약물복용 관리, 그리고 장기이식코디네이터의 합병증 관리, 일상생활에서의 감염관리, 추후 정기적인 외래 방문과 혈액검사의 중요성 그리고 문제발생시 이식팀과의 연락방법 등이 포함된다.
- 특히, 간이식 후 초기에 할 수 있는 근력운동을 교육하여 근육 감소를 방지하도록 한다.

퇴원 후 관리

- 퇴원 후 환자는 정기적인 외래진료를 통해 약물복용이행 등의 자가관리 확인, 혈액검사를 통한 거부반응, 감염상태, 그리고 면역억제제 약물농도 등의 결과를 확인 받고 수술상처나 배액관 등을 점검 받게 된다.
- 퇴원 초기에는 거부반응이나 감염 등의 문제로 재입원하는 기회가 높으므로 이러한 상황을 자각할 수 있는 증상에 대한 교육이 특히 필요하다.
- 매년 정기적인 암 조기검진이 되도록 교육한다.

간이식은 수술과 동시에 평생 동안 면역억제제를 복용해야 하고 건강을 유지 증진하기 위한 자기관리를 하는 노력이 필요하고 간이식 수혜자의 자기관리를 증진시키기 위해서는 간이식 수혜자의 유능성을 증대시키고 현재의 건강상태를 긍정적으로 인식할 수 있도록 지속적인 교육이 필요하다.

환자교육은 환자의 불안을 감소시키고 환자의 만족감을 증진 시킨다는 교육의 효과에 관한 많은 연구들이 있고 특히 간이식후 1년은 사회 적응을 위한 준비단계로 퇴원 후 적응을 위한 교육이 집중적으로 필요한 시기이기도 하므로 환자 교육에 좀 더 세심한 관심을 기울일 필요가 있겠다.

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The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 2: Friday, June 21, 2019 (08:30-09:30)
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KLCA Symposium 1

A Developing Strategy to Improve Diagnosis of HCC

Chairs:

Jin Wook Chung (Seoul National Univ.)
June Sung Lee (Inje Univ.)

Surveillances for HCC in Patients with Non-Alcoholic Fatty Liver Disease

Vincent Wong

The Chinese University of Hong Kong, Hong Kong

Nonalcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide and affects around a quarter of the adult population in Asia-Pacific countries. Nonalcoholic steatohepatitis (NASH) is the active form of NAFLD with hepatic necroinflammation, more rapid fibrosis progression, and a higher risk of adverse clinical outcomes. While hepatocellular carcinoma (HCC) only affects a small fraction of NAFLD patients, the total number of cases can still be substantial when one multiplies the risk of HCC and the huge number of patients. As a result, NASH has already become the third most common cause of HCC in the United States. The number of patients undergoing liver transplantation for HCC secondary to NASH has also increased by 4-fold from 2002 to 2012.

Data on NASH-related HCC in Asia are scarce. In a study of 6508 Japanese patients with NAFLD diagnosed by ultrasonography, only 16 (0.25%) developed HCC at a median follow-up of 5.6 years. Although this may suggest that NASH-related HCC is unimportant in Asia-Pacific countries, we should not forget that this problem has only been emerging recently even in western countries. Since it takes decades before chronic liver diseases progress to cirrhosis and HCC, it is possible that there will be a time lag before we witness the wave of NASH-related HCC in Asia.

Although cirrhosis is one of the most important risk factors of HCC for most chronic liver diseases, a number of reports suggest that up to a third of NASH-related HCC develop from non-cirrhotic livers, a figure higher than that in other liver etiologies. There are several possible explanations for this phenomenon. First, there is some overlap in the signaling pathways of NASH and HCC. NASH may thus directly promote HCC development. Second, the proportion of NAFLD patients with cirrhosis is lower than that in other liver diseases. It comes as no surprise that non-cirrhotic HCC is also more common in NAFLD patients. Finally, some patients with NASH-related cirrhosis may be classified as cryptogenic cirrhosis when hepatic steatosis is no longer apparent. In any case, non-cirrhotic HCC has major clinical implications; it would be difficult to define a high risk group for HCC surveillance.

Are Emerging Biomarkers and Imaging Tools Better than Routine Abdominal Sonography for HCC Surveillance?

Do Young Kim

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The reasons why prognosis of hepatocellular carcinoma (HCC) is poor along with pancreas cancer and lung cancer among solid cancers are decreased liver function due to accompanied hepatitis or cirrhosis and advanced stage at the time of diagnosis.[1] Thus, the rate of application of curative treatments is not high. The way of increasing patient survival is to diagnose HCC as early as possible. The guidelines by Korean Liver Cancer Association (KLCA)/National Cancer Center and other international or regional guidelines recommend surveillance for HCC of 6-months interval using liver ultrasonography (US) and serum alpha-fetoprotein (AFP) in patients who are at risk of developing HCC, such as those with cirrhosis, chronic hepatitis B (CHB) or chronic hepatitis C.[2-5]

For a method to be an effective surveillance one, the survival benefit should be proved. In only one randomized controlled trial conducted in China, there was 37% decrease of mortality in CHB patients who received surveillance using US + serum AFP compared to those who did not receive any surveillance. However, the study design and treatment algorithm were not appropriate, requiring a caution in the interpretation of results.[6] Nevertheless, the current surveillance strategy with US+serum AFP seems to be effective in the early diagnosis of HCC. However, we can not conclude that this strategy improves patient survival because the studies were from single cohort without control group.[7,8]

There is unmet need of developing imaging or novel biomarkers that can overcome the limitations of current US and serum AFP. In addition, there is also need of analyzing patient characteristics or morphological characteristics of liver in patients in whom it is difficult to diagnose early HCC, when applying US+serum AFP.[9,10]

There were efforts to apply magnetic resonance imaging (HCC) with hepatobiliary-specific agent or unenhanced MRI in HCC surveillance to overcome the limit of US.[11-13] Although it is obvious that these advanced imaging techniques can find early HCC which might not be detected by the current US, it is still controversial that enhanced or unenhanced MRI meet the criteria for HCC surveillance tool.

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Is LI-RADS Better for Diagnosis of HCC?

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Hepatocellular carcinoma (HCC) can be diagnosed based on characteristic findings of arterial-phase enhancement and portal/delayed "washout" in cirrhotic patients. Several countries and major academic societies have proposed varying specific diagnostic criteria for HCC, largely reflecting the variable HCC prevalence in different regions and ethnic groups, as well as different practice patterns. In 2018, a new version of Korean practice guidelines for management of HCC was released by the Korean Liver Cancer Association (KLCA) and the National Cancer Center (NCC). In addition, the LI-RADS 2018 version was integrated into the HCC diagnosis, staging, and management practice guidance of the American Association for the Study of Liver Diseases (AASLD). Furthermore, Asian-Pacific Association for the Study of Liver (APASL) and European Association for the Study of the Liver (EASL), changed the HCC guidelines with the advances in the imaging techniques in 2017 and 2018, respectively. The Liver Imaging Reporting and Data System (LI-RADS®) is a comprehensive system for standardizing the terminology, technique, interpretation, reporting, and data collection of liver observations in individuals at high risk for hepatocellular carcinoma (HCC). In this lecture, I will briefly review the new HCC diagnostic criteria endorsed by the 2018 KLCA-NCC Korea practice guidelines, in comparison with other recent guidelines, with special emphasis on the currently published LI-RADS algorithms.

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KLCA General Meeting (K*)

0202 Liver Cancer Day Special Lecture

Hyun Woong Lee

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제3회 간암의 날 (2월 2일); 비만과 간암의 관계

이 현 웅

연세대학교 강남세브란스병원 소화기내과

Background & Aim: In this systematic review and meta-analysis, we aimed to clarify the effect of obesity on the occurrence of and mortality from primary liver cancer.

Methods: This study was conducted using a systematic literature search on MEDLINE, EMBASE, and the Cochrane Library until November 2018 using the primary keywords "obesity," "overweight," "body mass index (BMI)," "body weight," "liver," "cancer," "hepatocellular carcinoma," "liver cancer," "risk," and "mortality." Studies assessing the relationship between BMI and occurrence of or mortality from primary liver cancer including hepatocellular carcinoma in prospective cohorts and those reporting hazard ratios (HRs) or provided data to allow HR estimation were included.

Results: A total of 28 prospective cohort studies with 8,135,906 subjects were included in the final analysis. These included 22 studies with 6,059,561 subjects for cancer occurrence and 7 studies with 2,077,425 subjects for cancer-related mortality. In the meta-analysis, an increase in BMI was associated with the occurrence of primary liver cancer (HR 1.69, 95% confidence interval [CI]: 1.50-1.90, I2 = 56%). A BMI-dependent occurrence of primary liver cancer was reported. HRs were 1.36 (95% CI: 1.02-1.81), 1.77 (95% CI: 1.56-2.01), and 3.08 (95% CI: 1.21-7.86) for BMI > 25 kg/m^2, > 30 kg/m^2, and > 35 kg/m^2, respectively. Furthermore, increased BMI resulted in enhanced liver cancer-related mortality (HR 1.61, 95% CI: 1.14-2.27, I2 = 80%).

Conclusion: High BMI increases liver cancer mortality and occurrence of primary liver cancer. Obesity is an independent risk factor for the occurrence of and mortality from primary liver cancer.

매년 2월 2일은 대한간암학회가 제정한 "간암의 날"이다. 2월 2일로 제정한 이유는 간암을 조기진단하기 위한 건강검진을 1년에 2번, 간암표지자인 AFP과 복부초음파 검사 2가지를 규칙적으로 시행하자는 의미이다.

간암은 한국인에게 많이 생기는 암 중 하나이다. 연령표준화발생률을 기준으로 살펴보면, 2015년에는 10만명당 남자 29.5명, 여자 8.2명으로 남성에서 4위, 여성에서 6위를 차지하고 있다. 특히 암사망률이 높아 2015년 전체 암사망자 중 간암이 남성에서 2위, 여성에서 3위를 차지하고 있다. 특히 사회적으로 경제적 생산성이 높은 중년의 사망률이 높다는 점에서 간암은 국가적으로 큰 영향을 미치는 질환이 아닐 수 없다. 비록 과거 자료이지만, 2005년 간암으로 인한 사회경제적 부담은 2조 4,552억원으로 2조 3,963억원의 위암을 추월하고 1위를 차지하였으며, 암환자 1인당 부담 역시 6,700만원으로 췌장암에 이어 2위를 차지하였다. 간암은 상대적으로 사망

률이 높고, 더 젊은 나이에 사망하기 때문에 이로 인한 사회적 부담은 전체 암 중 가장 크다.

최근 들어 비만이 암 발생과 밀접한 관련이 있다는 보고가 많이 되고 있다. 우리나라의 비만 유병률은 2016년 기준 34.8%이며, OECD는 우리나라 고도 비만인구가 2030년 지금보다 두 배 늘어날 것으로 예상하였다. 특히 비만으로 인한 지방간이 우리나라에서 흔한 만성 B형, C형간염 환자 들에서 간경변증 및 간암 발생을 증가시킬 수 있다는 점을 고려한다면 비만이 국내 간암 발생에 미치는 영향은 더욱 커질 수 있다.

이에 대한간암학회는 제3회 "간암의 날"을 맞이하여 〈비만과 간암의 관계〉라는 주제 하에 비만이 간암에 미치는 영향 등에 관해 발표하였다. 2019년 대한간암학회가 비만과 간암의 관계에 대한 28개의 연구논문을 메타분석하였다.[1-10] 비만한 사람의 경우, 그렇지 않은 사람보다 간암 발생률이 1.69배 높고, 간암 사망률 역시 1.61배 높았다. 특히 비만한 정도가 심할수록 간암 발생률 및 간암 사망률이 비례하여 증가하였다. 체질량지수 25(kg/m^2)이상인 경우 간암 발생률이 1.36배, 체질량지수 30 (kg/m^2)이상인 경우 1.77배, 체질량지수 35 (kg/m^2)이상인 경우 3.08배 높았다. 간암 사망률 또한 체질량지수 25 (kg/m^2)이상인 경우 1.25배, 체질량지수 30 (kg/m^2)이상인 경우 1.37배, 체질량지수 35 (kg/m^2)이상인 경우 2.82배 높았다(그림 1). 특히, 간암 발생의 고위험군인 바이러스간염 환자의 경우에도, 비만한 경우 비만하지 않은 경우보다 간암 발생률이 1.76배 증가하며, 체질량 지수가 증가할수록 그 위험이 증가하는 것으로 나타났다. 바이러스간염 환자의 경우 체질량지수가 25 (kg/m^2)이상인 경우 간암 발생률이 1.49배, 체질량지수가 30 (kg/m^2)이상인 경우 간암 발생률이 2.07배 높았다.

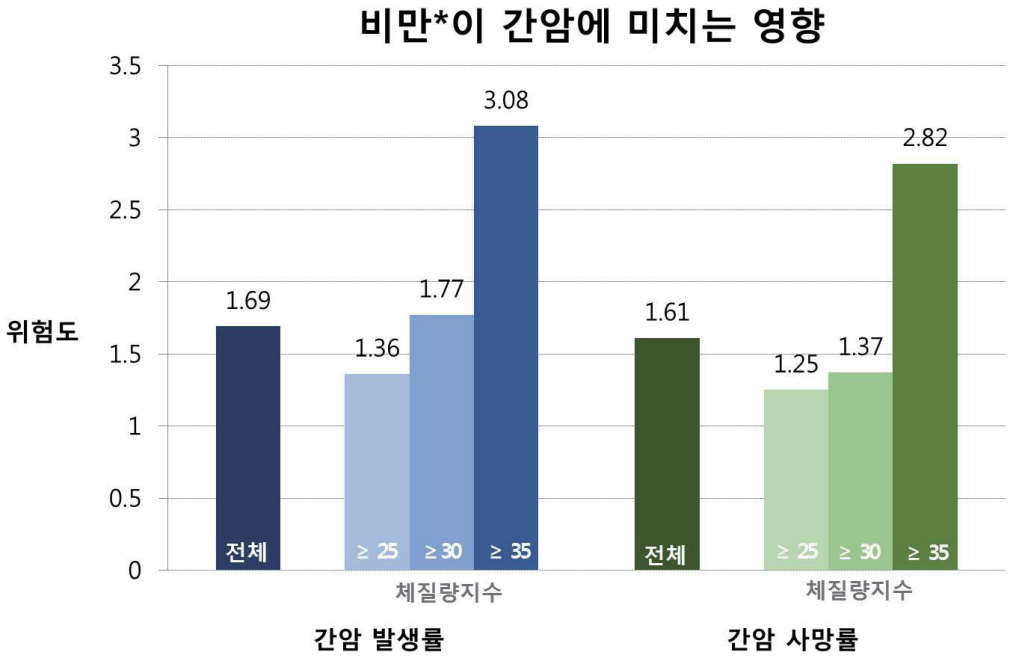

그림 1. 비만이 간암에 미치는 영향

이상을 정리하면, 비만은 간암의 발생과 사망률에 중요한 위험인자이며, BMI 25 이상의 비만은 간암의 발생과 사망률을 증가시킬 수 있고, 비만이 심해질수록 간암의 발생과 사망률은 더욱 증가한다. 또한, 만성 바이러스성 간염이 비만과 동반되면, 간암의 발생률을 증가시킨다.

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DAY 2: Friday, June 21, 2019 (13:30-14:30)
ROOM D [2F] 205

LCSGJ-KLCA Joint Symposium 1

One Step Forward for Understanding Basic Knowledge

Chairs:

Yutaka Kawakami (Keio Univ., Japan)
Young Nyun Park (Yonsei Univ.)

Potential of Exosome-Carrying microRNAs in Liquid Biopsy

Takahiro Ochiya

Department of of Molecular and Cellular Medicine, Tokyo Medical University, Tokyo Japan

Rapid advances in liquid biopsy techniques in recent years have led to research on the use of extracellular vesicles (EVs), in the diagnosis of diseases. The attraction of EVs as novel biomarkers is that they are present in various bodily fluids including blood, urine, saliva and breast milk, while disease-specific EVs have a high concentration among pathology-specific molecules. The analysis of EV biomarkers in blood or other fluid samples would enable preliminary diagnosis of diseases where tissue samples are difficult to obtain, and would eliminate the need for the direct tissue sampling of conventional biopsies, which would in turn be effective in reducing unnecessary biopsies. Meanwhile, the concentrated molecules in disease-specific EVs could be used together with diagnostics to promote personalized medicine. However, a number of issues need to be clarified and resolved, such as developing an EV liquid biopsy test for clinical use and identifying the molecules that make up disease-specific EVs. Here we will also present our current progress on EV-mediated circulating microRNAs for early detection of 13 species of cancer including HCC and dementia in Japan.

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T Cell Based Adoptive Cell Therapy for Solid Cancers

Yutaka Kawakami

International University of Health and Welfare (IUHW) School of Medicine, Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Japan

Cancer immunotherapy particularly immune-checkpoint inhibitors (ICIs) (anti-PD-1/PD-L1 and CTLA-4 Ab) have recently been established as one of the standard cancer therapies for a variety of cancers. However, the responses to ICIs are still limited (response rates are about 10-20%). Thus, the identification of biomarkers to select appropriate patients and appropriate immunotherapies as well as the improvement of immunotherapy efficacy possibly through combination strategies or T cell based adoptive cell immunotherapy (ACT) are needed.

The response to immunotherapies depends on immune status of patients particularly in tumor microenvironment (TME), which is defined by cancer cell genetic characteristics (e.g. immunogenic DNA mutations, immunosuppressive oncogenes and aneuploidy), patients' genetic immune-reactivity (e.g. immune related gene SNPs, HLA types), and environmental factors (e.g. intestinal microbiota, smoking, UV, diet/obesity, stress). In general, for the patients with cancer cells having sufficient immunogenic antigens such as neo-antigens, ICI based combination immunotherapies may be effective, but for the patients without immunogenic antigens, gene engineered T cells (e.g. chimeric antigen receptor (CAR-T) or T cell receptor (TCR) gene transduced T cells) may be useful. Therefore, in addition to various ICI based combination immunotherapies, we have been developing T cell based ACTs including tumor infiltrating T lymphocyte (TIL) therapy for metastatic melanoma and chemo-resistant advanced cervical cancer, and CAR-T or TCR-T therapies for various solid cancers including hepatocellular carcinoma (HCC).

Anti-tumor T cells can be generated and expanded sufficient for clinical use from TILs of melanoma and cervical cancer. Clinical trials of ours and others showed that TIL therapy was effective for about 30% of melanoma patients even who failed to previous ICI therapy. For patients with other types of cancer, we have been developing CAR-T therapy targeting to two different tumor antigens. One of the CAR-Ts we are developing is targeting to human glypican-1 (GPC1), which is a cell surface molecule expressed on various cancers including lung cancer. GPC1 specific CAR-T showed strong tumor regression activity in both human cancer implanted xenogeneic tumor model and murine syngeneic tumor model. Furthermore, combination of anti-PD-1 Ab with GPC1-CAR-T was found to be more effective than either treatment alone.

For HCC patients, PD-1 Ab has been approved in the US, and combination immunotherapies such as PD-1/PD-L1 Abs plus anti-VEGF Ab or VEGF-R inhibitors are currently being evaluated. Transcriptome analyses of HCC tumor tissues defined immunological subtypes and suggested that some of the patients with either viral or non-viral cancers are T cell inflamed (relatively significant $CD8^+$ T cell responses) and may respond to PD-1/PD-L1 inhibitor monotherapies, but others are T cell non-inflamed and may not respond to PD-1/PD-L1 inhibitors. In one of the T cell non-inflamed subtypes, stem cell like subtype, cancer cells express high amount of cell surface glypican-3 (GPC3). Then, we have also developed CAR-T targeting to human GPC3 which may be useful for the patients with ICI resistant stem cell like HCC subtype. These T cell based ACTs may be attractive strategies for the patients with various cancers including advanced HCC which may be resistance to various drug therapies including ICIs.

Oncolytic Virus-Based Therapy for HCC

Jeong Heo

Department of Internal Medicine, College of Medicine, Pusan National University, Busan, Korea

Oncolytic virotherapy (OVT) is the treatment using oncolytic viruses (OVs) for cancer. OVs are designed to replicate selectively in and destroy directly cancer cells and induce immune responses (Russell et al., *Nature Biotechnology*. 2012). Almost OVs are engineered viruses, selectively infect cancer cells including adenovirus, herpes virus, measles virus and vaccinia virus (VV) (Lichty et al., *Nature Reviews Cancer*. 2014). Telomelysin is engineered telomerase-specific replication competent oncolytic adenovirus, shown not only objective clinical responses, but also immune reactions in various solid tumors (Nemunitis et al., *Mol Ther.* 2010). Pexa-Vec (JX-594) is a Wyeth strain oncolytic VV, also shown both responses in HCC (Heo et al., *Nature Medicine.* 2013). OVs can be adopted into cancer immunotherapies. As recent developments and applications of immunology in cancer treatment, immune checker-points inhibitors (ICIs) including anti CTLA4 Ab, anti PD-1 Ab and PD-L1 Ab have been tried for various cancers including hepatocellular carcinoma. The limitations in efficacy of ICIs are related to poorly immunogenic tumors and highly suppressive tumor microenvironment (TME) (Liu et al.,*Oncoimmunology*. 2016 and Fend et al., *Cancer Research*. 2017). OVs would lyse cancer cell and cause the release of various antigen, cytokine including type 1 interferon, which induce antitumor immunity and enhance T cell recruitment in non-immunogenic and immune-deserted TME. The combination strategies both OVT and ICIs would enhance the efficacy, safety and cost-effectiveness, compared to each alone treatment, in terms of dosages and treatment interval. OVs in various combination therapies have been evaluated for therapeutic efficacy in preclinical as well as clinical levels, which could affect almost all aspects of the cancer–immunity cycle, recruit tumor infiltrating lymphocytes to the TME and transform non-immunogenic and immune-deserted tumor into immune-competent tumor. The strategy of OVs and ICIs combination have increased therapeutic responses. The selection of virus, optimal dosing, route of administration and schedule in oncolytic virus treatment require further study. Clarification between tumor-specific T cell responses and the contribution of viral-specific T cell responses should be further investigated. The versatility and safety of oncolytic viruses would be the ideal agents for optimizing combination immunotherapy.

DAY 2: Friday, June 21, 2019 (14:30-15:30)
ROOM D [2F] 205

LCSGJ-KLCA Joint Symposium 2

Similarities and Differences in Treatment of HCC

Chairs:

Shoji Kubo (Osaka City Univ., Japan)
Seung Kew Yoon (The Catholic Univ. of Korea)

Recent Trends of Treatment for Intermediate Stage HCC: Japanese Experience

Masatoshi Kudo

Kindai University Faculty of Medicine, Osaka, Japan

Although transcatheter arterial chemoembolisation (TACE) is the standard of care for intermediate-stage hepatocellular carcinoma (HCC), there is a subgroup of patients who do not benefit from TACE. The treatment strategy for this subgroup of patients currently remains an unmet need. We performed a proof-of-concept study that lenvatinib may be favorable treatment as an initial treatment in intermediate-stage HCC patients with large or multinodular tumours exceeding the up-to-seven criteria.

This proof-of-concept study included 176 patients who received lenvatinib or TACE as an initial treatment and met the eligibility criteria [beyond the up-to-seven criteria, no prior TACE, no vascular invasion, no extrahepatic spread and Child-Pugh A]. Propensity score matching was used to adjust for patient demographics.

After propensity-score matching, outcome of 30 patients prospectively treated with lenvatinib (14 in clinical trials, 1 in early access program and 15 in real world setting) and 60 patients treated with cTACE as the initial treatment was compared. The change of ALBI score from baseline to the end of treatment were -2.61 to -2.61 for 30 patients in lenvatinib group ($p = 0.254$) and -2.66 to -2.09 in cTACE group ($p < 0.01$), respectively. The lenvatinib group showed a significantly higher objective response rate (73.3% vs. 33.3%; $p < 0.001$). Overall survival was significantly longer in the lenvatinib group than in the cTACE group (37.9 vs. 21.3 months; hazard ratio: 0.48, $p < 0.01$).

In patients with intermediate-stage HCC beyond the up-to-seven criteria with Child-Pugh A, who usually do not benefit from TACE, lenvatinib provides more favorable outcome than TACE.

Recent Trends of Treatment for Intermediate Stage HCC: Korean Experience

Ji Hoon Kim

Korea University College of Medicine, Seoul, Korea

Intermediate stage of hepatocellular carcinoma (HCC) in BCLC class is including very heterogeneous patients group in terms of not only liver function, but also tumor size. Therefore, same intermediate stage of HCC patients received different treatment modality and showed diverse prognosis. For example, HCC patient with four tumors in lateral lobe and child score 5 could receive surgical resection and might get good prognosis. However, HCC patient with four tumors in both lobe and child score 7 could receive TACE and the prognosis might be somewhat dismal compared with the patients described above.

Because of this heterogeneity, BCLC has been challenged to be the optimal staging method and many researcher including Bolondi L have been tried to optimize intermediate stage of BCLC. Moreover, BCLC recommended only TACE for proper treatment in intermediate stage of HCC patients. However, as I mentioned above, HCC patients with intermediate stage BCLC could receive surgical resection and could receive ablative therapy or liver transplantation sometimes. These practice for intermediate stage HCC patients generally showed diversity between nations.

In this LCSGJ-KLCA Joint Symposium, I will present past and current Korean experience of treatment of HCC patients with intermediate stage.

Recent Trends of Treatment for Advanced Stage HCC: Japanese Experience

Kazuomi Ueshima

Kindai University Faculty of Medicine, Osaka, Japan

In Japan, 4 molecular targeted agents are approved and available for hepatocellular carcinoma. Sorafenib and lenvatinib are the first-line agents and regorafenib and ramcirumab are the second-line agents. However, the immune checkpoint inhibitor nivolumab and pembrolizumab are not approved in Japan unlike Korea. For one year since lenvatinib was approved in March 2018, over 10,000 HCC patients have been treated with lenvatinib. Lenvatinib has changed clinical practice for advanced HCC dramatically. Clinically the first choice of treatment for advanced HCC with Child-Pugh A is almost lenvatinib due to its high response rate, different toxicities from sorafenib and its good cost-effectiveness. If the down-staging is obtained, loco-regional therapy such as resection, RFA or TACE is added radically. If lenvatinib is failed, sorafenib-regorafenib sequential therapy is performed but its effectiveness are limited. There is no second-line treatment for the patients who failed to lenvatinib but ramucirumab may be the candidate of effective second line treatment because of high activity of inhibition against VEGFR2 with high serum concentration. Ramucirumab may also be the standard agent for elderly patients due to its less toxicity. On the other hand, molecular targeted agents are not recommended for patients with Child-Pugh B, therefore hepatic arterial infusion chemotherapy or TACE as a loco-regional therapy is selected in case the patients have extrahepatic metastases if intrahepatic lesion is prognostic factor. The systemic chemotherapeutic agents for the patients with Child-Pugh B are now warranted. The effectiveness of nivolumab for Child-Pugh B HCC was reported. In the near future, nivolumab may be the first line agent for Child-Pugh B HCC.

Recent Trends of Treatment for Advanced Stage HCC: Korean Experience

Won Young Tak

Internal medicine School of Medicine Kyungpook National University, Korea

Liver cancer is the third leading cause of cancer-related deaths worldwide, and hepatocellular carcinoma (HCC) represents 70% to 90% of all liver cancers. The burden of HCC is increasing worldwide. It's incidence and mortality rates have been steadily increasing. The crude annual rate of liver cancer mortality has increased over the last 30 years in Korea. Systemic therapies are indicated for advanced stage of HCC, not indicated for surgery or locoregional treatments. Systemic therapies include conventional cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy. Molecularly targeted therapies are the current mainstream of systemic therapy in Korea.

Sorafenib is the first approved molecularly targeted therapy agent for the treatment of advanced hepatocellular carcinoma and that targets vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), and Raf/MEK/ERK. The Asia Pacific trial, phase III study, was the first sorafenib trial for the advanced HCC that included Korean patients. In the Asia Pacific trial, median overall survival (OS) was 6.5 months in patients treated with sorafenib, compared with 4.2 months in those who received placebo (hazard ratio [HR] 0.68 [95% CI 0.50-0.93]; P=0.014). Based on these results, sorafenib approved as first-line systemic chemotherapy for advanced HCC in Korea.[1] The GIDEON study was a large-scale observational study involving 3,171 patients from 39 nations who were treated with sorafenib. The Gideon study reported that Median OS was different according to Child-Pugh class: 13.6 months for class A, 6.2 months for B7, 4.8 months for B8, and 3.7 months for B9.[2] The Korean subset of the Gideon study, which included 497 patients from 11 sites, reported the median OS and time to progression (TTP) were 8.5 months and 2.5 months. In Child-Pugh A patients, the median OS and TTP were 10.2 months and 2.5 months. The most common adverse effects associated with sorafenib include hand-foot skin reaction (HFSR), diarrhea, hypertension, rash, fatigue, abdominal pain and nausea. The Korean data of the Gideon study reported that the most frequent treatment-emergent drug-related adverse event was hand-foot skin reaction (31.7%), followed by diarrhea (18.0%) and the safety profile did not appear to differ by Child-Pugh status.[3]

Regorafenib is a multikinase inhibitor that targets kinases involved in angiogenesis, oncogenesis, and the tumour microenvironment. We participated in phase II and phase III clinical trials. But the Korean data of these trials were not separately analyzed. The RESORCE trial, phase III study, included patients who progressed after sorafenib treatment with Child-Pugh A and an ECOG score 0-1. Regorafenib improved OS with an HR of 0.63 (95% CI, 0.50 to 0.79; $P < 0.0001$); median survival was 10.6 months (95% CI, 9.1 to 12.1 months) for regorafenib versus 7.8 months (95% CI, 6.3 to 8.8 months) for placebo. Adverse events were reported in all regorafenib recipients (374 [100%] of 374) and 179 (93%) of 193 placebo recipients. The most common grade Grade 3 or 4 adverse events were hypertension (15%), HFSR (13%), fatigue (9%), and diarrhea (3%) in regorafenib group. Based on this result, regorafenib was approved as second-line systemic therapy who progressed after sorafenib treatment.[4] In subgroup analysis of patients from Asia, OS, PFS, TTP and treatment emergent adverse events were similar to overall patients.

Another multikinase inhibitor, lenvatinib, recently demonstrated non-inferiority of OS compared with sorafenib as first-line therapy for unresectable HCC. In phase III trial for advanced HCC patients with a tumor occupying less than 50% of the liver and no bile duct or main portal vein invasion, median OS was 13.6 months (95% CI, 12.1 to 14.9 months) for lenvatinib and 12.3 months (95% CI, 10.4 to 13.9 months) for sorafenib. The most common any-grade adverse events were hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%), for lenvatinib.[5] Based on these results, lenvatinib approved as first-line systemic chemotherapy for advanced HCC in Korea

Nivolumab is a IgG4 anti-PD-1 (programmed cell death receptor-1) monoclonal antibody and works as an immune checkpoint inhibitor. A non-comparative phase I/II trial for patients with advanced HCC demonstrated an overall ORR of 20% (complete response 1%, partial response 18%) and a duration of response of 9.9 months.[6] In subgroup analysis, median OS of sorafenib-experienced asian patients (n = 85), included 13 Korean patients, was 14.9 months. Currently, a randomized controlled multicenter phase III trial comparing nivolumab and sorafenib as first-line treatment for advanced HCC (CheckMate-459, ClinicalTrial.gov ID: NCT025276509) is ongoing.

In Korea, Sorafenib is approved for advanced stage of HCC with Child-Pugh class A and ECOG score 0-1. Lenvatinib is also approved for advanced stage of HCC not indicated for surgical resection. Regorafenib is approved for patients with progressive HCC after sorafenib treatment and with Child-Pugh class A and ECOG score 0-1. Nivolumab approved for patients with progressive HCC after sorafenib with Child-Pugh score 5 to 7. In Korea, many of the systemic therapy experience was from clinical trials and the real world data is limited except sorefenib.

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DAY 2: Friday, June 21, 2019 (16:30-17:50)
ROOM D [2F] 205

KLCA Symposium 2

New and Emerging Systemic Therapies in Advanced HCC

Chairs:

Kwang-Hyub Han (Yonsei Univ.)
Seung Woon Paik (Sungkyunkwan Univ.)

First Line Treatments for HCC

Arndt Vogel

Department of Gastroenterology, Hepatology and Endokrinology, Visceralonkologic Centre, Medizinischen Hochschule Hannover (MHH), Germany

Hepatocellular carcinoma (HCC) ranks among the most common and deadliest cancers worldwide. Incidence rates nearly doubled over the last decades and, to date, HCC is one of the fastest growing causes of cancer related deaths in the USA. Despite effective surveillance options less than 20% of patients are eligible for curative treatment, such as liver transplantation, resection, or radiofrequency ablation, at the time of diagnosis. During the past 10 years, drug development in advanced HCC stages has been significantly hampered by a pronounced phenotypic and molecular heterogeneity of the tumors, as well as a high toxicity of active compounds under clinical evaluation. The majority of patients with advanced HCC presents with a severely impaired liver function, which further requires a fine balance between anti-tumor activity and drug-induced toxicity. This lecture will summarize primary efficacy data and clinically relevant post-hoc analysis of the pivotal first-line phase-III trials in HCC.

Until recently, the multi-tyrosinekinase inhibitor sorafenib was the therapeutic standard of care in a first line setting since 2007. Median overall survival (OS) in the sorafenib arm was 10.7 months vs. 7.9 month in placebo-treated patients. Similar results were not only demonstrated in a parallel phase III study involving mainly Asian, predominantly hepatitis B-infected patients, but also in 8 subsequent phase III studies in which sorafenib served as control treatment. Notably, although currently no predictive biomarkers for response exist, several clinical factors including chronic hepatitis C infection or side effects including early dermatological events or hypertension favor a better response to the treatment

Lenvatinib is another oral multi-tyrosinkinase inhibitor with activity against VEGFR1-3, FGFR1-4, PDGF, RET und KIT. The RESOURCE phase III study involving mainly Asian patients was conducted to demonstrate a non-inferiority of lenvatinib in comparison to sorafenib in a first line setting. The study achieved its primary endpoint with a median OS of 13.6 months in the experimental lenvatinib arm versus 12.3 months in the sorafenib arm (HR: 0.92; 95% CI 0.79-1.06). An interesting observation of this trial was the high objective response rate (ORR) for lenvantinib with 24.1% vs 9.2% for sorafenib despite the similar OS (independent review: ORR mRECIST 40.6% vs. 12.4%, ORR RECIST: 18.8% vs. 6.5%). Further, surrogate characteristics for survival such as progression free survival (PFS), Time-to-Progression (TTP) were consistently higher in the lenvatinib group than in the sorafenib group (PFS: 7.4 months vs. 3.7 months; TTP: 8.9 months vs. 3.7 months). Importantly, the study excluded patients with adverse prognostic tumor characteristics, e.g. main branch portal vein thrombosis or >50% tumor occupation of the liver. Nevertheless, results from the trial encourage the use of lenvatinib as an effective first line therapy in advanced HCC leading to inclusion in recent EASL and ESMO guidelines. Consequently, approval for lenvatinib in first line was recently granted by the FDA and EMA.

Second Line Treatments for HCC

Stephen L. Chan

Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong

An expanding number of drug treatment is available for advanced HCC, which include multi-targeted TKI, checkpoint inhibitors and monoclonal antibody. Following failure with first-line treatment, lenvatinib or Sorafenib, a number of second-line treatment has become available, including regorafenib, cabozantinib and PD-1 antibody. Ramucirumab has also been recently approved by US FDA for treating AFP-positive HCC in second-line setting. There are no head-to-head comparison amongst these second line treatments hence the decision is based on the mechanism of action, clinical trial data, toxicity of each agent.

A Future of Systemic Agents: Emerging Therapies and Strategies

Baek-Yeol Ryoo

Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Hepatocellular carcinoma (HCC) develops in the condition of uncontrolled growth of hepatic cells caused by the genetic alterations in complex signaling cascades. Therefore, we can expect the effect of targeted agents attacking important targets in carcinogenic pathways along with minimizing general adverse effects. However, we have failed to find the dominant signal pathways in hepatocarcinogenesis, yet.

Sorafenib is a multikinase inhibitor especially inhibiting serine/threonine kinases Raf-1/B-Raf, tyrosine kinases VEGFR-2/-3 and PDGFR-β, which suppresses cancer progression and angiogenesis. Sorafenib is the first systemic therapy prolonged survival significantly in HCC patients. After that sorafenib not only established a proof of concept for the use of multi-kinase inhibitors strategy for the treatment of HCC, but also is the reference standard for systemic therapy for HCC patients.

Nevertheless, subsequent clinical trials using targeted agents have failed in succession for about 10 years. The agents which failed to prove their activity in HCC were sunitinib, linifanib, brivanib, nintedanib in the first-line treatment and axitinib, ramucirumab, brivanib, erlotinib, everolimus, tivantinib, ADI-PEG20 in the second-line treatment after sorafenib failure.

Recently, lenvatinib, another angiogenesis inhibitor, showed non-inferior overall survival in the 1st-line treatment compared with sorafenib in the REFLECT trial. Lenvatinib also showed rather superior response rate, progression free survival, time to progression and preferable toxicity profiles.

For the patients who failed sorafenib treatment, regorafenib and cabozantinib, mainly angiogenesis inhibitors overcame placebo control in RESORCE and CELESTIAL trials.

In addition, nivolumab showed meaningful results for HCC in phase II checkmate 040 trial.
We have now 2 options in the 1st-line and 3 options after sorafenib failure in HCC, with angiogenesis inhibitor or immune checkpoint inhibitor.

However, the current effects of systemic treatments for HCC are far from satisfaction as ever.
By looking at the trials currently conducted for HCC, we are discussing ways to improve the prognosis of HCC patients.

Combination of Interventional and Systemic Therapies for HCC: Current Status and Future Direction

Joong-Won Park

National Cancer Center, Korea

Combination therapy, a modality that combines more than one type of therapy or agent simultaneously or sequentially, is an effective cancer therapy. The rationale for combination therapy is to use drugs or modalities that work by different mechanism, thereby increasing the chances of a cure or long-term remission. Surgery or locoregional therapy (LRT) treats cancer that is confined locally, while systemic therapy kills the cancer cells that have spread to distant sites. Combination therapy can be generally useful for people with advanced cancers. Sometimes broad definition of combination therapy includes neoadjuvant therapy and adjuvant therapy.

For improving the outcomes of hepatocellular carcinoma (HCC) treatment, a various combination of surgery, LRT such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), radiofrequency ablation (RFA) and external beam radiation therapy (EBRT), and systemic therapy is attempted. In HCC therapy, unfortunately, the combination of systemic therapies has not yet been sufficiently validated. Combination therapy with TACE and systemic agents (sorafenib) has not proven to be superior to systemic agent alone, but some patients may benefit from combination therapy.

Theoretically, LRTs can increase tumor immunogenicity, which can result in an increase of tumor infiltrating cytotoxic T cells with systemic antitumor immune response. However, the evidence of this hypothesis is poor yet. Fortunately, initial results from studies combing LRTs with immunotherapies demonstrated especially promising results.

The combination of LRTs with systemic therapies may further improve response and survival rates in HCC treatment, and may change the current paradigm of HCC therapy.

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 3: Saturday, June 22, 2019 (09:00-10:00)
ROOM A [1F] 103-105 / 108-110

Symposium 3

Hepatitis C Virus

Chairs:

Masao Omata (Yamanashi Prefectural Central Hospital, Japan)
Si Hyun Bae (The Catholic Univ. of Korea)

Long-Term Outcome of Direct-Acting Antiviral Treatment

Jung Il Lee

Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

만성 C형 간염에서 Direct-Acting Antiviral을 이용한 치료의 장기적 예후에 대한 고찰

이 정 일

연세대학교 의과대학 내과학교실

만성 C형 간염의 치료는 direct-acting antivirals (DAAs)의 개발과 함께 비약적인 발전을 보여, 거의 95% 이상의 지속바이러스반응을 보이게 되었다. 그러나 DAA에 의한 C형 간염 바이러스 박멸이 간암과 같은 간질환의 장기적인 예후에 미치는 영향에 대해서는 아직 연구 및 증거가 더 필요한 실정이다. 그러나 최근에 보고된 대규모 전향적인 코호트 연구결과에 따르면 DAA 치료는 만성 C형 간염 환자에서 간암 발생을 감소시키며 생존율을 증가시키는 것으로 생각된다. 그러나 이미 간암이 발생한 만성 C형 간염 환자에서의 DAA 치료에 대해서는 추가적인 연구가 필요할 것으로 생각된다.

It has been reported that eradicating hepatitis C virus (HCV) infection decreases the liver related morbidity and mortality, reduces the risk of hepatocellular carcinoma (HCC) and improves the survival.[1] Although direct-acting antivirals (DAAs) are very effective in the treatment of chronic HCV infection, its long-term benefits are still not clear. In addition, there has been some controversial reports over whether DAA therapy would increase the risk for HCC shortly after DAA treatment.[2]

Recently, there has been a prospective cohort study reporting clinical outcomes in over 7,000 patients with chronic HCV after DAA treatment.[3] The study demonstrated that HCV patients after DAA treatment would have decreased risk for liver-related mortality as well as reduced risk for HCC. When the analysis was performed for those with HCV related liver cirrhosis, DAA treatment in HCV patients could still reduce the risk for liver-related mortality and HCC development.

Nevertheless, further investigations may need in determining the benefits of DAA treatment in HCV patients that already experienced HCC. A recent study on early HCC patients after curative treatment suggested that DAA treatment would improve survival.[4] However, another study recruiting cirrhotic patients that showed complete response to HCC treatment failed to demonstrat reduced HCC recurrence after DAA treatment.[5] Another study suggested that the effect of DAA induced SVR on HCC occurrence might take time, and would not change the short-term HCC risk after DAA treatment.[6]

Conclusion

It seems that DAA induced SVR would reduce liver-related mortality by reducing liver-related complication including HCC. However, beneficial role of DAA treatment as secondary prevention of HCC might need more evidences to draw a conclusion.

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Follow-Up Strategies Following Cure of Hepatitis C Virus Infection

Naoya Sakamoto

Department of Gastroenterology and Hepatology, Hokkaido University Faculty of Medicine, Japan

There are 71 million chronic hepatitis C (CHC) patients, in which a significant number of those develop cirrhosis or liver cancer. Approximately 399,000 people die each year from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (HCC). Viral eradication after interferon (IFN)-based therapy has been associated with an improvement of liver function and a reduced risk of developing HCC in CHC patients. The IFN-free direct-acting antiviral (DDA) combinations can cure more than 95% of CHC patients, thereby hopeful of the reducing the risk of death from liver cancer and cirrhosis.

Nevertheless, in the early years of their use, there are some negative reports on the effectiveness of DAA therapy in the recurrence of HCC. Following the reports of larger prospective studies, the risk of de novo HCC occurrence has been proven clearly to be lower after the achievement of sustained virological response (SVR), regardless of antiviral treatment. On the other hand, the risk of HCC recurrence following DAA treatment is controversial. The possible alterations in the immune system after clearance of the virus with the DAAs and how they may affect the conventional cancer immunity cycle are still under discussion. The aim of this presentation is to review published data on the risk of HCC occurrence and recurrence after viral eradication and provide an update on the risk and benefit of DAAs treatment revealed by clinical and basic researches so far.

Unmet Needs in the Era of Direct-Acting Antiviral Therapy

Ming-Lung Yu

Department of Internal Medicine, Kaohsiung Medical University and Hospital, Taiwan

Since the first directly acting antivirals (DAA) approved in 2011, the progress of DAA in HCV treatment is moving from IFN (IFN)-containing regimens to IFN-free regimens in 2013, which are currently standard-of-care. Currently, there are 14 DAAs approved in the treatment of HCV and at least 9 major combination regimens are applied in the clinical practice for HCV treatment. The two pan-genotypic DAA regimens sofosbuvir/velpatasvir and glecaprevir/pibrentasvir could cure all genotype with SVR rate of 96-99%.

However, even with such high SVR rate, there remains many unmet needs after SVR achieved:

1) The HCC risk remains. There are conflict data addressing the risk of HCC occurrence or recurrence after SVR by IFN-free DAA versus IFN-based regimens. Unexpected higher HCC risk after SVR by IFN-free DAA have been reported in Spain and France. By contrast, recent large scaled study from US and Japan did not observed higher HCC risk after SVR by IFN-free DAA. Nevertheless, even the risk of HCC is greatly reduced by achievement of SVR, a substantial number of patients remain at high risk of HCC, such as advanced fibrosis, old age, diabetes and persistently high levels of alfa-fetoprotein or liver enzymes. Recent studies demonstrated that HCV-induced epigenetic changes associated with liver cancer risk persist after SVR, suggesting HCC remains an unmet need after SVR.
2) The progression of hepatic decompensation after SVR remains among patients who have Child-Pugh class B or C decompensated liver cirrhosis before DAA therapy. These patients are still unable to de-listing from liver transplantation, especially for those with MLED score > 20.
3) Extrahepatic manifestations, although decreased in prevalence after SVR, will persist among substantial proportion of HCV patients after SVR, and need life-long monitoring/care.
4) Although current DAA regimens could achieve very high SVR rates of > 98%. The DAA failed patient number will accumulate year by year. The multiple drug resistance HCV strains will be very difficult-to-cure population in the near future.
5) Barriers to HCV elimination: Low disease awareness and accessibility in the care cascades of HCV treatment are the major hurdle on the way to HCV elimination. Finally, lack of HCV vaccine, HCV would never be controlled.

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State-of-the-Art Lecture 2

Chair:
Jin Mo Yang (The Catholic Univ. of Korea)

Current Understanding of Autoimmune Liver Diseases

Atsushi Tanaka

Teikyo University School of Medicine, Tokyo, Japan

Autoimmune liver diseases (AILD), autoimmune hepatitis (AIH), primary biliary cholangitis (PBC; formally known as primary biliary cirrhosis), and primary sclerosing cholangitis (PSC), have been considered to be a relatively uncommon etiology in Asia, where viral hepatitis is the diagnosis in the majority of patients with chronic liver diseases. However, recent findings demonstrate that prevalence of autoimmune liver diseases is increasing worldwide and therefore the importance of improving recognition and management of these diseases is increasing in Asia as well. In Korea, Professor Sook-Hyang Jeong, one of my best friend and colleague, published excellent papers regarding epidemiological studies of PBC and AIH in Korea. Recently, our group also published an increasing trend of prevalence of AIH, PBC and PSC in Japan.

The etiology of AILD are multifactorial, and involves the interaction of both genetic background and environmental triggers. Environmental insults in genetic susceptible individuals can develop aberrant immunological reactions and lead to autoimmune-mediated hepatocyte or bile duct injuries, indicating that AILD results from the combination of "bad genes and bad luck". As innovative progresses of state-of-the-art techniques for identifying disease-susceptible genes such as genome-wide association studies (GWAS), a number of genes have been identified as contributing to development or progression of AILD. Despite the identification of genetic susceptible loci, it still remains obscure how these genetic elements can account for the pathological development of these diseases. Furthermore, a number of case-control studies, including a very recent study in PBC from Korea which is the first one in Asia, have identified several risk factors in the environment. Recent epidemiological studies clearly demonstrate a significant change in male-to-female ratio of patients with AIH and PBC, suggesting the alteration of environmental triggering factors for development over time.

From the clinical standpoint, it is crucial to always keep in mind the possibility of AILD in differential diagnosis when encountering patients with elevated liver enzymes. Detection of anti-mitochondrial antibody (AMA) in patients with chronic elevation of cholestatic enzymes establish a diagnosis of PBC. Since disease-specific biomarkers are lacking in AIH, a combination of exclusion of viral hepatitis, detection of anti-nuclear antibody (ANA), and typical histopathology are required to make a diagnosis of AIH. Similarly, characteristic cholangiographic findings such as band-like stricture and beaded or pruned-tree like appearance with presence of inflammatory bowel diseases in patients with chronic cholestasis are important for diagnosis of PSC.

Corticosteroids and ursodeoxycholic acid (UDCA) are established as first-line treatment options for AIH and PBC, respectively, while 20-30% of patients require second-line treatment due to incomplete responses or intolerance to the first-line. Azathioprine and mycophenolate mofetil are recommended as second-line therapy for AIH, and currently a phase 2/3 clinical trial with anti-BAFF receptor (VAY736) for AIH patients with incomplete responses to corticosteroids is underway. A very recent study from an international collaborative PBC study group (Global PBC group) indicated that PBC patients with incomplete responses to UDCA exhibited a significantly better prognosis compared to those without UDCA treatment, again unravelling the efficacy of UDCA. Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist, was approved for PBC with incomplete responses to UDCA in the US and Europe. In Japan,

bezafibrate has been used for those with incomplete responders. The efficacy of bezafibrate was recently confirmed by a randomized controlled study in France, and we also demonstrated a long-term efficacy of bezafibrate with a large-scale retrospective cohort in Japan. On the other hand, no medical treatment including UDCA has been proved to be effective for improving liver transplantation (LT)-free survival in PSC, and recurrence of PSC after LT seriously deteriorate long-term outcome. Nevertheless, a recent phase 2 clinical trial of Cilofexor (GS-9674), a non-steroidal FXR agonist, for non-cirrhotic PSC patients was very promising, and a global phase 3 trial will soon be launched. Another promising candidate drug for PSC is *nor*URSO, a side chain-shortened C23 homologue of UDCA, which are or will be on global clinical trials including Asia.

Taken together, a series of new and promising drugs are coming in sight as novel treatment options for AILD, making individualized treatment possible based on stratification of risk for progression, and significantly improving overall survival as well as quality of life of patients. At the same time, global, Asian, and Korea-Japan collaborations is definitely warranted for more understanding of AILD.

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DAY 3: Saturday, June 22, 2019 (14:30-15:40)
ROOM A [1F] 103-105 / 108-110

Symposium 4

Cirrhosis

Chairs:
Rino Gani (Univ. of Indonesia, Indonesia)
Soon Koo Baik (Yonsei Univ. Wonju)

Mesenchymal Stem Cell Therapy for Liver Cirrhosis - Basic Study and Clinical Application -

Shuji Terai

Division of Gastroenterology & Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Japan

Liver cirrhosis, caused by chronic inflammation followed by fibrosis, is one of the prevalent refractory diseases in Japan, with more than 400,000 people suffering. Thus, a new therapy supporting liver fibrosis regression and regeneration, which the liver is inherently capable of, is urgently required. We started a clinical study for decompensated cirrhosis using autologous bone marrow cells in 2003 (Autologous Bone Marrow infusion, ABMi therapy). From the clinical study, we found BMC infusion improved liver cirrhosis and induced liver regeneration. ABMi therapy is effective for liver cirrhosis patient. Bone marrow cell included both mesenchymal stem cell (MSC) and macrophage, so we analyzed the mechanism of how and which bone marrow cell is effective to improve liver cirrhosis. In basic study with mice model using two photon microscopy, MSCs migrate to the lung work as "Conducting cells", and bone marrow-derived macrophages that migrate to the damaged fibrotic liver area and change its polarity through interaction with MSCs function as "Effector cells". Exosomes are critical as communication tools between MSCs and macrophages. Injecting only exosomes can achieve liver fibrosis regression and regeneration similar to MSC injection. On the other hands, we proceed Phase I/II clinical trial using allogeneic adipose tissue-derived mesenchymal stem cells (MSCs) for decompensated cirrhosis in 2017.

In this presentation, I will present status of MSC therapy for liver cirrhosis.

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The Role of Albumin Related with Systemic Inflammation in Cirrhosis

Paolo Angeli

Unit of Internal Medicine and Hepatology (UIMH), University of Padova, Italy

Albumin was introduced in the treatment of patients with cirrhosis and ascites to increase the reduced plasma oncotic pressure, which, at that time, was thought to be a pivotal factor together with portal hypertension, in the pathogenesis of ascites. The following evolution of the knowledge showed that the renal functional abnormalities in cirrhosis are the final consequence of a reduction of effective circulating volume due to a marked splanchnic arterial vasodilatation. As a consequence, the rationale of the use of albumin in patients with cirrhosis and ascites was completely changed. Albumin is no more used on the basis of the plasma albumin concentration but in clinical situations that are or are going to be a sign of severe reduction of effective circulating volume such as: 1) prevention of post-paracentesis circulatory dysfunction, 2) prevention of hepatorenal syndrome in patients with spontaneous bacterial peritonitis (SBP), and 3) treatment of hepatorenal syndrome.

Albumin is very effective in preventing of post-paracentesis circulatory dysfunction and of hepatorenal syndrome in cirrhotic patients with SBP. In addition, albumin administration improves survival in patients with spontaneous bacterial peritonitis. In the treatment of hepatorenal syndrome, the use of albumin in combination with vasoconstrictor drugs is essential for the recovery of renal function and to improve slightly survival. More recently, it has been observed in a multicentre Italian RCT that albumin is capable to improve survival also in patients with responsive ascites. In these patients albumin reduces not only the rate of development of refractory ascites but also of SBP, infections other SBP, hyponatremia, hepatic encephalopathy and renal impairment. For sure, these effects can be due not only to its oncotic properties as plasma but to its several non-oncotic effects also. In particular, in the setting of SBP, albumin exerts a positive on cardiac output. Experimental and clinical data showed that the increase in cardiac output induced by albumin is not only related to its effect on cardiac pre-load but also to a cardiac positive inotropic effect. The inotropic effect of albumin in rats with cirrhosis and ascites was related to its effectiveness in counteracting the negative effects of oxidative stress- and TNF-α-induced activation of NF-kB-iNOS pathway and oxidative stress-induced alteration of β-receptor signaling in the cardiac tissue.

It seems easy to foresee that the role of albumin in the management of patients with cirrhosis and ascites will be once more defined in the near future.

Role of Cytoglobin, a Novel Radical Scavenger in Stellate Cell Activation and Hepatic Fibrosis

Norifumi Kawada

Osaka City University Medical School, Japan

Cytoglobin (CYGB) belongs to the globin family and is expressed in hepatic stellate cells (HSCs). In addition to its gas-binding and radical scavenging ability, we have been demonstrated that CYGB deficiency induced spontaneous fibrosis and cancer development in aged mouse liver and augmented their manifestation in mice treated with DEN- or CDAA-diet. On the other hand, HSC-specific overexpression of CYGB-mCherry protected mice from TAA-triggered liver fibrosis. These results obtained by *in vivo* studied confirmed that CYGB is an important molecule for maintenance of HSCs in a quiescent status. While we have been searching for molecules that triggered CYGB induction in human HSCs, we noticed that FGF2 is a key factor in inducing the alteration in both CYGB and αSMA expression in human HSCs. FGF2 initiated the phosphorylation of both JNK and c-JUN. C-JUN overexpression up- and down-regulated *CYGB* and αSMA expression, respectively. In ChIP analyses, phospho-c-JUN bound its consensus motif located -218 to -222 bases from the transcription initiation site in the CYGB promoter upon FGF2 stimulation. In contrast, TGFβ1 antagonized the effect of FGF2 via SMAD2-SP3 passway. In conclusion, CYGB is likely a critical molecule relevant to the maintenance of quiescent phenotype of human HSCs.

DAY 3: Saturday, June 22, 2019 (09:00-10:00)
ROOM BC [1F] 101-102

KAHBPS Symposium 1

Surgical Research in HBP Field– Challenges and Barriers

Chairs:

Il-Young Park (The Catholic Univ. of Korea)
Koo Jeong Kang (Keimyung Univ.)

Surgeon-Scientists: An Endangered Species?

Sundeep G. Keswani

Department of Surgery, Pediatrics & OB/Gyn, Baylor College of Medicine and Children's Hospital, USA

Over the past several decades, federal funding to surgeon-scientists has been lagging, and our analysis suggests that this trend continues. This compounded by the current funding environment and its impact on research productivity, the future of basic research in academic surgery may be threatened. As the cost associated with conducting basic research continues to grow, the competition to obtain funding from the NIH and other extramural sources has become progressively difficult. This is especially true when considering the steady decline in the NIH pay line since 2003.

Although "success" in basic research is difficult to define, we use federal funding as a proxy, but accept that alternative revenue sources (private industry, philanthropy, clinical revenue) can sustain productive basic research programs. Nevertheless, achieving peer-reviewed federal funding is commonly accepted as indicative of a successful research effort. Based on this metric and the data presented previously by others, surgeon-basic scientists are falling behind and the future of this important aspect of academic surgery is uncertain. Recognizing that multiple challenges confront surgeon-scientists, the SUS formed a Basic Science Committee tasked with identifying the issues facing surgical investigators to inform potential solutions. In this talk, we will elucidate the findings of this committee that were published in the Annals of Surgery.

The changing academic and hospital environment has contributed to a prevailing perception that it is unrealistic for surgeons to succeed as basic scientists, and may have surgeons wondering whether it is even worthwhile to maintain and develop links between basic science and surgery. If such attitudes permeate surgical leadership, it will influence the justification for making the investment required to encourage young faculty along a path toward basic science inquiry and research independence. Current models for surgical training need to be evaluated and possibly changed to develop surgeon-scientists prepared to succeed in today's competitive scientific environment. If we agree that fundamental investigation into the pathophysiology and treatment of surgical disease needs to include the active participation of surgeons, then academic surgery must act to address these challenges and ensure continued development of surgeon-scientists and the environment that promotes their success or we run the risk of becoming an "endangered species".

Basic/Translational Research: How to Start and Grow?

Say-June Kim

Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

Firstly, I recommend that you write up a schedule with a series of milestones to accomplish by a specific date, and keep to it. You will need time to get an overview of what material is out there, find out what's in your library, select relevant material, read it, take notes, and start putting it together — and to do a second wave of research to clear up points raised in the writing of your first draft. Next, have a research question in mind. Technically, your thesis should emerge from your research, when you have data in front of you. But you need a kind of "working thesis" while doing your research — a question you want to answer. As you come across new material, ask yourself if it looks like it will help you answer your question. Anything that looks relevant but doesn't help answer your question you can put back. It's tempting to gather a lot of background material, and some is necessary, but too much will waste your time without contributing to your research. Get one or two good sources for background and then keep focused by working towards an answer to your research question. Start your research with an idea of how you plan to collect and organize your notes and data. Use the human resources available to you as well as the material resources. Ask for help in finding and evaluating sources, or for help in figuring out what to do with the material you've collected so far.

Clinical Research to Reduce Pancreatic Fistula after Distal Pancreatectomy

Manabu Kawai, Seiko Hirono, Kenichi Okada, Motoki Miyazawa, Yuji Kitahata, Ryohei Kobayashi, Masaki Ueno, Shinya Hayami, Hiroki Yamaue

Second Department of Surgery, Wakayama Medical University, Japan

Objective: The appropriate pancreatic stump closure during distal pancreatectomy (DP) remains still controversial. Three clinical trials including one multicenter randomized controlled trial (RCT) have been conducted to evaluate the most appropriate pancreatic stump closure during DP.

Evaluation of stapler closure: In the first study, the risk factors of pancreatic fistula were investigated among three types of stump closure; hand-sewn suture (n=32), bipolar scissors (n=45), and stapler closure (n=45) in 122 DP. There was no significant difference regarding pancreatic fistula between the three types of stump closure (hand-sewn suture: 44% vs. bipolar scissors: 37.7% vs. stapler closure: 35.5%). However, this study reported that pancreas thicker than 12 mm significantly increased pancreatic fistula after DP using stapler closure.

Evaluation of pancreaticojejunostomy for pancreatic stump during DP: Second, a multicenter RCT (NCT01384617) was performed to evaluate whether pancreaticojejunostomy (PJ) of pancreatic stump decreases pancreatic fistula after DP compared to stapler closure. One hundred thirty-six patients were enrolled. Pancreatic fistula occurred in 23 patients (37.7%) in stapler closure group and 24 (38.7%) in PJ group (P=0.332) in intention-to-treat analysis. The incidence of clinically relevant pancreatic fistula was 16.4% for stapler closure and 9.7% for PJ (P=0.201). In a subgroup analysis for thickness of pancreas >12 mm, clinically relevant pancreatic fistula occurred in 22.2% of the patients in the stapler closure group and in 6.2% of the PJ group (P=0.080). This study could not clarify the impact of PJ for pancreatic stump. However, PJ for pancreatic stump might offer a potential reduction of pancreatic fistula in cases with thicker pancreas.

Evaluation of reinforced stapler during DP: In last multicenter single-arm, prospective, nonrandomized study (NCT02270554), 121 patients for DP were enrolled to evaluate whether reinforced stapler decreases clinically relevant pancreatic fistula after DP. Per-protocol analysis was performed using 105 patients. Clinically relevant pancreatic fistula occurred in 13 (12.4%) of 105 patients. Severe complication (Clavien classification IIIa or more) was 10.5% (11/105). Multivariate analysis revealed that staple line hemorrhage (P=0.006, odds ratio 8.6) were an independent risk factor for clinically relevant pancreatic fistula after DP. This study concluded that reinforced stapler did not reduce clinically relevant pancreatic fistula after DP.

Conclusion: As further steps adequately powered prospective randomized trials should be required to evaluate the most appropriate pancreatic stump closure during DP.

DAY 3: Saturday, June 22, 2019 (10:20-11:20)
ROOM BC [1F] 101-102

KAHBPS Symposium 2

Clinical Issues in Non-Hepatic Abdominal Surgery in Patients with Liver Cirrhosis

Chairs:

Hyung Chul Kim (Soonchunhyang Univ.)
Yang Won Nah (Univ. of Ulsan)

Management of Gallstones and Acute Cholecystitis in Patient with Liver Cirrhosis - Medical Treatment: Indication and Result of Medical Treatment -

Ki Tae Suk

Department of Internal Medicine, Hallym University College of Medicine, Korea

Cholesterol gallstone disease is a common clinical condition influenced by genetic factors, increasing age, female gender, and metabolic factors. Although laparoscopic cholecystectomy is currently considered the gold standard in treating patients with symptomatic gallstones, new perspectives regarding medical therapy of cholelithiasis are currently under discussion, also taking into account the pathogenesis of gallstones, the natural history of the disease and the analysis of the overall costs of therapy. A careful selection of patients may lead to successful nonsurgical therapy in symptomatic subjects with a functioning gallbladder harboring small radiolucent stones. The classical oral litholysis by ursodeoxycholic acid has been recently paralleled by new experimental observations, suggesting that cholesterol-lowering agents which inhibit cholesterol synthesis (statins) or intestinal cholesterol absorption (ezetimibe), or drugs acting on specific nuclear receptors involved in cholesterol and bile acid homeostasis, might be proposed as additional approaches for treating cholesterol gallstones. In this review we discuss old, recent and future perspectives on medical treatment of cholesterol cholelithiasis.

Keywords: Cholesterol, Stone, Cirrhosis

담석 질환 (Gallstone disease)은 세계의 많은 지역에서 흔히 발생하는 질환이다. 담석은 선진국 인구의 10-15 %에 발생한다.[1] 화학적 구성과 관련하여 담석에는 콜레스테롤과 색소(pigment)의 두 가지 유형이 있습니다. 콜레스테롤 담석은 선진국에서 담석의 주요 유형을 나타냅니다. 많은 경우에 담석은 하나 또는 다른 성분의 우위와 혼합되어 있습니다. 색소 담석은 담즙성 감염 또는 용혈 상태의 환자에서 발생하는 갈색 담석 (감염성) 환자에서 검은 담석(대사성)으로 나뉜다.

간경변은 만성간질환의 최종 단계로 규명하며 서양 국가에서 보편적인 질병으로 널리 퍼져 있다. 이는 비만 및 대사증후군, 알코올, 바이러스 간질환의 발현으로 간염이 원인 질환이 되며, 미국과 유럽에서 C 형 간염바이러스 감염이 1970 년대 이후에 발생했고 가장 많은 발병 원인으로 알려져 있다.[2]

간경변으로 이어질 수 있는 많은 간질환 중 급속하게 (년) 진행되고 다른 일부는 더 천천히 (수십 년) 진행된다. 담석은 대개 간경변의 지속 기간이 길면 발병하며 간경변 환자의 담석 유병률은 일반 인구의 2 배 이상인 25 %에서 30 % 사이이다.[3]

치료

무증상의 담낭의 내과적인 치료

증상 또는 합병증이 발생할 위험이 적기 때문에 일반 인구에서 무증상 담석을 가진 환자에게 기대하는 치료가 적절한 권장사항이다. 담낭절제술은 수술적인 절차로 증상이나 합병증을 일으키지 않는 환자에서는 우선적으로 고려하지 않는다.[4]

무증상의 담석이 있는 간경변 환자에게도 똑같은 권고가 적용된다. 간경변 환자의 무증상 담석은 증상이나 합

병증이 발생할 경우 가까이에서 모니터링하고 수술하며 보존적으로 관리하는 것이 가장 좋다. 진행된 간질환이 있을 때 수술 위험이 높아질수록 담석이 진단될 때 환자와 논의해야하며 치료 결정에 적극적으로 참여해야 한다.

내과 치료

증상이 경미하고 전형적인 담도성 통증을 의심하기 어려운 경우나, 환자가 수술을 원하지 않거나 혹은 수술을 시행하기 어려운 경우에는 내과적인 치료를 고려할 수 있다. 현재 담낭 담석의 치료에 시도해볼 수 있는 비수술적 방법에는 담석을 용해시키는 방법으로 경구 담석용해제 또는 담낭 안에 직접 약물을 주입하여 담석을 용해시키는 방법이 있고, 담석을 분 쇄, 제거하는 방법으로 체외충격파 쇄석술과 경피경간 담낭경을 이용하여 담석을 제거하는 방법이 있다. 그러나 최근 20년 간 복강경 담낭절제술이 보편화되면서 내과 치료의 비중이 감소하고 있는 추세여서 이들 중에서는 일부 환자에서 경구 담석용해제를 투여하는 것 외에 나머지 치료는 치료 효과에 비하여 비용이나 합병증의 발생 위험이 높아 최근에는 거의 시행되고 있지 않다.

경구 담즙산 제제

경구 담즙산 제제는 담석의 용해요법에 가장 많이 사용되는 약물로 chenodeoxycholic acid (CDCA)와 ursodeoxycholic acid (UDCA) 등이 흔히 사용된다. 1972년 처음으로 CDCA가 방사선 투과성 담석의 용해에 이용되기 시작하였고 이후 1975년 친수성 담즙산인 UDCA가 CDCA의 부작용 없이 이를 대치하여 담석 용해에 이용되게 되었다. 경구 담즙산 용해요법의 근거는 콜레스테롤 담석의 형성 과정에서 가장 중요한 기전이라고 할 수 있는 담즙내 콜레스테롤의 과포화를 억제시키는데 있다.[5]

CDCA나 UDCA를 경구로 투여하면 담즙산 저장고의 상당 부분이 CDCA나 UDCA로 대치되면서 담즙산 저장고의 용량이 확장되고, 콜레스테롤의 담즙내 분비는 억제되어 담즙내 콜레스테롤의 포화도가 감소하게 된다. 이렇게 콜레스테롤이 불포화된 담즙이 분비되어 담낭 내로 들어가 담석의 표면을 둘러싸면 담석 내의 콜레스테롤이 미포 (micelle) 내로 용해되어 나오게 되어 담석의 용해가 일어나게 된다.

경구 담즙산 제제는 작용기전을 고려할 때 방사선 투과성 콜레스테롤 담석만을 용해시킬 수 있고 담석의 칼슘 성분이 많을수록 용해되기 어렵기 때문에 순수한 콜레스테롤 담석보 다는 색소성 담석의 비중이 높은 우리나라에서는 환자의 선택이 용이하지 않다. 담석 용해를 위한 CDCA의 효과적인 투여 용량은 13-15 mg/kg/day인데, 최소 치료용량 이상의 용량에서 설사, 간기능 장애, 혈청 콜레스테롤 상승 등의 부작용이 흔히 발생하여 현재는 담석용해 치료로 CDCA의 단독투여는 더 이상 추천되지 않는다. 대신에 CDCA의 합병증을 줄이고 치료효과를 높이기 위하여 CDCA와 UDCA (각 5-8 mg/kg/day)의 병합요법이 이용되며, 국내에서도 CDCA 114 mg과 UDCA 114 mg의 복합제제(씨앤유®; Myungmoon Pharm. Co. Ltd, Seoul, Korea)가 시판되고 있다. 한편 UDCA는 친수성 담즙산으로 간 혹은 장내세균에 의하여 형성되는 3차 담즙산이다. UDCA 는 장에서의 콜레스테롤 흡수와 담즙으로의 콜레스테롤 분비를 억제하여 담즙내 콜레스테롤 포화도를 40-60% 감소시킬 수 있다.[6]

담석 용해를 위해서는 10-14 mg/kg/day의 용량을 투여하는데 식사 후나 자기 전에 투여한다. CDCA와는 달리 간독성이 적고 혈중 콜레스테롤을 상승시키지 않으며, 설사는 1% 이하에서 발생한다. 현재 가장 많이 사용되고 있는 경구 담즙산 용해요법은 UDCA 단독요법이고, UDCA와 CDCA 병합요법도 사용되고 있다. 경구 담즙산 용해요법은 담낭 기능이 정상인 방사선 투과성 콜레스테롤 담석에 효과가 있다. 용해 효과는 6-12개월 후 영상진단으로 평가한다. 용해 효과는 담석의 CT 영상에서 예측할 수 있으며 CT에서 60 HU 미만의 담석에서 용해 효과가 가장 좋은 것으로 알려져 있다.[7]

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Management of Gallstones and Acute Cholecystitis in Patient with Liver Cirrhosis - Surgical Treatment: What Should We Caution to Consider Surgery? -

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Surgical treatments, both laparoscopic cholecystectomy (LC) and cholecystectomy via laparotomy (OC), are the mainstream treatments of several conditions related to biliary origin currently, including pain due to cholecystolithiasis, gallbladder polypoid lesions, choledocholithiasis with or without cholangitis, acute cholecystitis, and biliary pancreatitis. In addition, the timing of surgical treatment to individual aforementioned condition has also been proposed. Based on one of our recent study, patients who underwent percutaneous gallbladder drainage for acute cholecystitis and declined to elective cholecystectomy later still would encounter high risk of recurrence (up to 30%) with a median time of less than 5 months. The role of cholecystectomy for symptomatic gallbladder stones, therefore, cannot be replaced by other conservative treatment and LC is considered as the gold standard.

Cirrhosis is one of the most complicated human diseases and makes significant changes in physiology, local alteration of anatomy, modification of immune status, and other associated risks, which influence life expectancy. When it comes to surgical treatment of cholelithiasis, patients with cirrhosis were exposed to additional risks from 3 aspects: (1) relatively higher risk of cholelithiasis than general population, (2) relatively higher surgical risk, regardless to surgical procedures, and (3) increase surgical difficulty related to local condition, such as abundant collateral vessels around surgical field. Our previous investigation revealed that LC, once considered contraindicated in patients with cirrhosis, is a feasible procedure for most Child's A and B patients with gallbladder stones and related conditions. Minor morbidity, an acceptable conversion rate, and shorter hospital stay can be achieved by applying LC to treat cirrhotic patients. However, appropriate preoperative preparations and meticulous operative techniques are required to reduce blood loss during laparoscopy and even mortality. Currently published studies, including retrospective case-controlled studies, prospective trials, and meta-analysis, also supported this point of view. In addition, LC is better than OC in several clinical aspects, including shorter operative time, reduced complication rates and reduced length of hospital stay. Considering to the possibility of future liver transplantation for cirrhotic patients, laparoscopic procedure may provide additional benefit of reducing postoperative abdominal adhesion, compared to open surgery. For the non-compensated cirrhosis, not only lack of study related to surgical outcomes (over 95% of currently reported cases were Child's A and B) and conservative treatment still favored.

During the last decade, several surgical innovations, such as techniques related to LC, energy devices, and other related products related to hemostasis, have provided surgeons an arsenal to conduct delicate procedures with better outcome, especially in the intraoperative bleeding control and bile duct injuries related to LC. Several studies have mentioned those interesting issues. Besides, improved perioperative management also guarantees a better quality of care.

In our presentation, we are going to share our previous experience in LC for cirrhotic patients, review the current relevant evidences, and discuss perioperative management and the impact from the advance in current surgical techniques related to LC on the cirrhotic patients.

Clinical Outcomes and Prognosis of Emergency Surgery in Liver Cirrhosis Patient

Fausto Catena

Parma University Hospital, Italy

The increasing incidence of advanced chronic hepatic disease among patients with acute abdomen represents a great challenge for the emergency surgeon.
The severity of liver insufficiency, the grade of portal hypertension, the type of emergency of surgery to be performed, and severity of other comorbidities are relevant predictors of postoperative mortality and morbidity.
Accurate patient history and examination together with scrupulous laboratory and imaging tests analysis are able to detect liver insufficiency with or without portal hypertension and all related affections.
A correct use of existing specific scores (Child-Pugh or MELD) consents to stratify patients' severity in order to timely treat all potential complications.
Coagulation disorders and hypovolemia are the most insidious intraoperative and postoperative challenges.
For this reason, during resuscitation it is mandatory a careful use of intravenous fluids and an appropriate targeted utilization of blood derivatives.
Two acute care surgery golden rules for high risk patients must be applied: first choose the quickest procedure, second use the less invasive operative strategy.
According to this policy laparoscopic techniques should be employed extensively.
Moreover, all new technologies such as a energy devices, staplers, hemostatics should be used without any concerns about costs.
Surgeons have to be aware about particular risks like severe bleedings from porto-systemic veins shunts even during abdominal wall dissection.
Liver and spleen anatomy can be different and standard surgical procedure such as splenectomy can be technically demanding in case of huge splenomegaly.
Finally, after surgery these patients in the postoperative course have an ongoing risk of liver/ renal insufficiency.

Elective Cancer Surgery in Patients with Liver Cirrhosis

Sae Byeol Choi

Korea University Guro Hospital, Seoul, Korea

Liver cirrhosis has been associated with increased postoperative mortality and morbidity. Therefore surgical indications in patients with cirrhosis were limited due to complications associated with portal hypertension Liver cirrhosis is a heterogenous disease, the severity of which has been evaluated with Child pugh score and MELD score.

In patients with liver cirrhosis, extrahepatic malignancy could be developed. Preoperative optiminization and evaluation of liver function as well as malignancy work up is essential to treat the malignancy. In this review, gastric cancer, colorectal cancer and periampullary cancers necessary pancreaticoduodenectomy or pancreas surgery are reviewed. In cancer surgery, the extent of surgery is expanded comparing with the operation for benign disease.

In gastric cancer, the standard surgery is gastrectomy with lymph node dissection. Radical operation with D1 or D2 lymph node dissection can be tolerated in class A gastric cancer patients. D1 lymph node dissection is recommended in class B patients, and radical gastrectomy is very dangerous, even fatal for class C patients. In Colorectal cancer patients with liver cirrhosis have poorer overall survival compared to those without liver cirrhosis; however, the recurrence rates are similar. It might be due to the mortality from the liver, and surgical treatment should be actively considered for patients with MELD-Na score <10. On the other hand, in periampullary cancers requiring pancreaticoduodenectomy or pancreas surgery, El Nakeeb et al haver reported surgical outcomes after pancreaticoduodenectomy in patients with liver cirrhosis. Patients with periampullary tumours and well-compensated chronic liver disease should be routinely considered for pancreatidoduodenectomy at high volume centers with available expertise to manage liver cirrhosis. Pncreatidoduodenectomy is associated with an increased risk of postoperative morbidity in patients with liver cirrhosis; therefore, it is only recommended in patients with Child A cirrhosis without portal hypertension.

The perioperative morbidity and mortality following non-hepatic surgical procedures in patients with cirrhosis are significant. Preoperative assessment of these patients for co-morbidities and liver function is essential if surgical outcomes are to be improved. Both Child score and MELD score is useful to prognosticate these patients in shorterm surgical outcomes.

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DAY 3: Saturday, June 22, 2019 (14:00-14:30)

ROOM BC [1F] 101-102

KAHBPS Special Lecture

Chair:

Hee Chul Yu (Chonbuk National Univ.)

The Journey from Scientific Idea to Funded Grant: A Surgeon's Approach

Sundeep G. Keswani

Department of Surgery, Pediatrics & OB/Gyn, Baylor College of Medicine and Children's Hospital, USA

In the morning lecture, we elucidated the challenges that are facing surgeons to become effective surgeon-scientists. Now that those problems are more defined, how does one begin the journey of taking your insightful surgical observations from an conceptual idea to a fundable proposal? Much like everything else that we do as surgeons it becomes better with practice, and it is facilitated when we have a methodologic approach to the procedure. Just like with any other surgery we will highlight and define an algorithmic approach to formulating a hypothesis and translating it into a grant that can be used in most scientific situations. This is a very extensive topic. However, this overview of taking an idea to a fundable proposal will give attendees a solid foundation on which to move your projects forward in order to make more impact. The overview will include how to generate a hypothesis, how to formulate appropriate specific aims to test a hypothesis, and then the components of most grants with an operative approach to achieving your goals.

DAY 3: Saturday, June 22, 2019 (14:30-15:30)
ROOM BC [1F] 101-102

KAHBPS Symposium 3

Focus Review of Advanced Gallbladder Cancer Treatment

Chairs:

Dong Wook Choi (Sungkyunkwan Univ.)
Sang-Jae Park (National Cancer Center)

The Operative Indication of Advanced Gallbladder Cancer: How Much Advance Is the Limitation?

Masayuki Ohtsuka, Hideyuki Yoshitomi, Katsunori Furukawa, Tsukasa Takayashiki, Satoshi Kuboki, Shigetsugu Takano

Department of General Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

Currently surgical resection is considered to be the only hope for long-term survival in patients with advanced gallbladder cancer (GBC) despite a recent improvement of non-surgical therapy. However, because the lesion is often advanced by the time of diagnosis, only a small subset of GBC patients qualifies for surgery.

In order to select patients eligible for surgical resection, both technical and oncological factors should be considered. Surgical resection for advanced GBC is recommended only if a potentially curative resection is possible. Therefore, cases with peritoneal dissemination or metastasis to distant organs other than the liver are contraindications for surgical resection. In addition, cases with invasion of the hepatic artery (HA) and/or portal vein (PV) to be unable to reconstruct, or cases with extensive hepatic invasion and/or liver metastasis to be unable to excise due to insufficient remnant liver volume are judged to be "technically unresectable". Excluded these cases, all patients with "technically resectable" disease should be potential candidates for surgical intervention.

However, advanced GBC often spreads to surrounding structures, such as the liver, the duodenum, the colon and the hilar structures (bile duct, hepatic artery, portal vein), and the prognosis of such cases is apparently poor even if radical surgical resection is achieved. In fact, our data indicates that the 5-year survival rate after surgical resection in 55 patients with advanced GBC (≥ T2) confined to the gallbladder is 46%, while it is only 20% in 64 GBC patients with a spread to extra-gallbladder. In particular, out of these 64 GBC patients with invasion to adjacent structures undergoing aggressive surgery with vascular and multivisceral resection, patients with obvious hepatic metastasis, patients with invasion of HA and/or PV requiring combined resection, and patients with invasion to more than three organs had significantly unfavorable prognosis. Curative resection was possible in only 9 of 15 patients with obvious hepatic metastasis, only 9 of 14 patients with invasion of HA and/or PV, and 10 of 15 patients with invasion to more than three organs. There were only three 2-year survivors in cases with obvious hepatic metastasis, only one in cases with invasion of HA and/or PV, and only one in cases with invasion to more than three organs. Therefore, advanced GBC cases with obvious liver metastasis, cases with invasion of HA and/or PV requiring combined resection, or cases with invasion to more than three organs should be regarded as "oncologically unresectable". This may be the limitation of surgical resection.

On the other hand, down-sizing chemotherapy has a potential to overcome this oncological limitation of surgical resection for advanced GBC. We experienced a patient with advanced GBC spreading to three organs such as the liver, the bile duct and the hepatic artery. This case was judged as "oncologically unresectable", so that chemotherapy was applied. After 4 courses of gemcitabine treatment, invasion of the hepatic artery was markedly improved, and surgical resection was performed. This patient survived more than 5 years. This strategy is expected to expand the surgical indication and to improve patient survival.

Recent Advances in the Chemotherapy in Advanced Gallbladder Cancer: Palliative vs. Neoadjuvant Chemotherapy

Hei-Cheul Jeung

Medical Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Gallbladder cancer (GBC) is the most common and aggressive malignancy of the biliary tree. GBC remains a highly lethal disease, with only 10% of all patients presenting at a stage amenable to surgical resection.

Systemic chemotherapy is the mainstay for the treatment of advanced biliary tract cancer. Combination of Gemcitabine plus cisplatin become the standard of care for advanced biliary tract cancer. However, chemotherapy has demonstrated modest survival prolongation effect in GBC and most published series are small and include heterogeneous population of patients with GBC, cholangiocarcinoma, and occasionally some pancreatic and hepatic cancers which respond differently to chemotherapy. Moreover, most studies reported are performed in patients with adenocarcinoma, the most common histology of GBC. There is paucity of data regarding treatment of advanced adenosquamous or squamous cell gallbladder cancers, and in clinical practice these patients are treated similarly. Reported overall response rates with chemotherapy in GBC patients are in the range of 50 to 60 percent. There is limited data assessing the impact of treatment on overall survival (OS). In the only randomized trial comparing chemotherapy (gemcitabine plus oxaliplatin [GEMOX] or 5-FU/leucovorin) against best supportive care alone in 81 patients with inoperable GBC, median OS was 4.5, 4.6, and 9.5 months in the supportive care, FU/leucovorin and GEMOX groups, respectively.

As for neoadjuvant therapy, currently outside the setting of a clinical trial, neoadjuvant therapy is not recommended for surgically resectable gallbladder cancer. Trials with a neoadjuvant strategy may provide opportunities for the development of predictive markers to guide personalized treatment in patients with gallbladder and biliary tract cancer.

Combination therapy using cytotoxics and molecular-targeted agents has been tested in GBC. However, its efficacy remains limited. It has not yet been clarified whether second-line chemotherapy can improve the prognosis of advanced GBC. Several problems exist when assessing the results of previous reports concerning advanced GBC. In the presentation, the current evidence in advanced of systemic therapy of GBC will be highlighted, and a view at possible future prospects linked with molecular profiling, immunotherapy, and targeted therapies will be provided.

Case Presentation

Chi-Young Jeong

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Background: Gallbladder cancer (GBC) is highly aggressive disease. Although surgical resection is the only curative treatment for GBC, multidisciplinary approach has received much attention in recent years.

Case presentation: The first case is 50 years old man. He underwent an extended cholecystectomy for GBC (pT2N2M0). We recommended adjuvant chemotherapy, but he denied. Sixteen months later, when a recurrence lesion was detected in peri-gastric area, we performed radical antrectomy, transverse colon segmental resection, segment 3,4 (s3,4) wedge resection and pancreas head partial resection. After surgery we started chemotherapy with gemcitabine and cisplatin. After a year of chemotherapy, the lesions suspected metastatic recurrence again appeared in para-aortic lymph node and we stared chemo-radiotherapy. After 8months of Chemo-radiotherapy, the para-aortic lesion decrease on imaging, but lesions suspected metastatic recurrence appeared in right adrenal gland, for which palliative chemotherapy was administered. The second case is 75 years old women. She underwent extended cholecystectomy with transverse colon segmental resection for GBC (pT3N1M0). We recommended adjuvant chemotherapy, but he denied. Four months later, the lesion suspected peritoneal seeding was detected. The third case is 66 years old man. In pre-operative image, GBC with liver invasion and multiple metastatic lymph nodes in periportal, perihepatic and para- aortic were detected. He underwent extended cholecystectomy for GBC (pT3N2M0). The fourth case is 66 years old man. He underwent extended cholecystectomy for GBC (pT3N0M0). We performed surveillance without further treatment. Since then, he has remained free of recurrent disease of 33 months follow up.

Conclusion: We hear report four cases of advanced GBC. The multidisciplinary treatment may be a promising option in selected patients with advanced GBC.

DAY 3: Saturday, June 22, 2019 (10:20-11:20)
ROOM D [1F] 106

Special Session

National Health Insurance Big Data Research (*K)

Chairs:

Hyoung-Soo Kang (National Health Insurance Service)
Jaeyoun Cheong (Ajou Univ.)

National Health Insurance Big Data Analysis: Process and Example

Seong Yong Park

Big Data Center, National Health Insurance Service, Korea

NHIS, as a single insurer, take responsibility for operation of National Health Insurance (NHI) scheme, such as eligibility review of the insured, imposition and collection of contributions, insurance benefit, and negotiation of medical fee schedule with healthcare service providers.

The Korean National Health Insurance Big Data (NHID) features a whole population cohort which can be used for research purposes. National Health Insurance Big Data is made out of many resources. Database of beneficiary, contributions, medical service utilization, health screening service, long-term care service is integrated into NHID through individual ID linkage.

National Health Insurance Big Data can be used in various areas. NHIS supports for research that contributes to evidence-based policies and provides customized health service and so on.

NHIS created a public research DB, only after a de-identification process, to improve the accessibility of data, and provides big data and support for research that contributes to evidence-based policies, relates to issues of public concern, and improves data availability, conducted by a professional societies or public institutions.

NHIS provides a various health services, such as one-stop service which includes an annual physical diagnosis, an assessment of potential health risks and a customized treatment plan to counteract any health risks, monitoring indicators for the prevention of cardiovascular disease, and a health map service for an adequate allocation of healthcare resources and design an effective system.

NHIS is expecting to prevent disease and cut medical costs and predict disease outbreak and improve overall health services using health big data. NHIS' final goal may be summarized that every people can live without the burden of disease. NHIS believes that the more trials we should put for exceeding the public data boundary lines, the faster our final goal can be accomplished.

National Health Insurance Big Data Research: HCC Surveillance

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국민보험공단 빅데이터를 이용한 간질환 연구: 간암 검진 연구

백 용 한

성균관대학교 의과대학 내과학교실

우리나라에서 간암은 2번째로 사망률이 높은 암종이며, 특히 40-50 대에서는 암관련 사망 원인 1위 질환으로, 간암으로 인한 사회적 손실이 매우 크다. 이러한 사회적 손실을 줄이기 위하여 2003년부터 간암 고위험군에 대한 국가 암조기검진사업이 시행되고 있다. 다른 암종과 달리 간암은 거의 대부분 고위험군에서 발생하므로 현재 우리나라에서는 40세 이상 만성 B형 간염, 만성 C형 간염, 간경변증 환자에 대하여 초음파 검사 및 혈청 alpha-fetoprotein (AFP)을 주기적으로 시행하고 있다. 그러나, 현재 시행되고 있는 국가 간암 검진의 현황 및 효과에 대하여 평가에 대한 연구는 부족한 실정이다. 이에 본 연구에서는 1) 국가간암검진을 포함한 간암검시검사의 수검 현황 및 패턴을 파악하고, 2) 고위험자들의 간암 발생 패턴 및 간암 감시검사로 인해 간암이 조기 발견되었는지 알아보고자 하며, 3) 간암감시검사로 인하여 생존율의 개선이 있었는지를 평가하고자 한다.

본 연구에서는 국민건강보험공단 빅데이터를 분석하여 간암감시검사의 효과 및 간암 환자의 예후를 향상시킬 수 있는 개선방향을 제시하고자 하며 크게 아래 두 가지 분석을 통하여 접근하고자 한다. 첫째는 2003년부터 2016년까지 국민보험공단 검진DB의 간암검진 자료를 이용하여 국가간암검진의 대상자분석을 통하여 수검률, 검진여부에 따른 조기간암 진단률, 검진여부에 따른 사망률 등을 분석하여 국가간암검진의 수검률 향상 및 사망률 감소를 위한 방향을 제시하고자 한다. 둘째로 국민건강보험공단의 맞춤형 데이터베이스를 이용하여 국가간암검진를 포함한 간암 감시검사 여부를 조사하여 간암 감시검사의 효과 및 개선방향을 분석하고자 한다.

이용 자료는 국민건강보험공단의 2002년부터 2016년까지의 건강보험청구자료와 국가암검진자료를 활용할 예정이다. 본 연구의 대상자는 40대 이상의 성인 중에서 2002년 시점에 간암 상병이 없고, 2003년부터 2016년 사이에 간암 고위험군 (간경변증, B형 간염바이러스 항원 양성, C 형 간염바이러스 항체 양성, B 형 또는 C형 간염 바이러스에 의한 만성간질환 환자) 으로 외래를 방문한 이력이 있는 환자를 대상으로 한다. 간암의 경우 간세포암 (C22.0)으로 정의하였고 조기 간암의 경우는 간암 관련 처치 중 간암을 진단 받은 후 처음 받은 치료가 수술 또는 고주파열치료술인 경우로 정의한다. 수검 패턴 및 수검 패턴에 따른 간암 발생을 분석하고 대상자의 특성 및 조기 간암 발생의 차이를 확인한다.

본 자료는 국가적으로 시행하고 있는 국가간암검진사업 및 간암감시검사를 평가하는데 중요한 근거가 될 수 있으며, 향후 관련 제도 개선 시에 활용할 수 있는 유용한 자료가 될 것으로 판단된다. 다만, 본 연구는 임상 변수가 제한적인 공공자료원을 이용한 연구이고, 환자들이 실제로 이용한 각각의 진료 기관과의 의무기록 연동이 불가하기 때문에 자료의 해석에 주의가 필요할 수 있다.

Role of Statins on Development and Progression of Non-Alcoholic Fatty Liver Disease: A Nationwide Nested Case-Control Study

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Objective: Use of statins in nonalcoholic fatty liver disease (NAFLD) may reduce cardiovascular morbidity, whereas their effects on NAFLD itself is not well known. We aimed to investigate the role of statins on development of NAFLD and progression of significant liver fibrosis.

Design: This study included 11,593,409 subjects from the National Health Information Database of the Republic of Korea, entered in 2010 and followed up until 2016. NAFLD was diagnosed by calculating fatty liver index (FLI) and significant liver fibrosis was evaluated using BARD score

Results: Among 5,339,901 subjects that had FLI <30.0 and included in non-NAFLD cohort, 164,856 subjects eventually had NAFLD developed and matched with 824,280 control subjects. Use of statin was associated with reduced risk of NAFLD development compared to that of the nonusers (AOR [adjusted odd ratio] 0.66; 95% CI [confidence interval] 0.65-0.67) in dose dependent manner, and independent of associated DM (AOR 0.44; 95% CI 0.1-0.46, with DM; AOR 0.71; 95% CI 0.69-0.72, without DM). From 712,262 subjects with FLI >60 and selected as NAFLD cohort, 111,257 subjects showed BARD score ≥2 and defined as liver fibrosis cases and matched with 556,285 control cases. Use of statins reduced risk of significant liver fibrosis compared to that of the nonusers (AOR 0.43; 95% CI 0.42-0.44) dose dependently, independent of DM (AOR 0.31; 95% CI 0.31-0.32, with DM; AOR 0.52; 95% CI 0.51-0.53, without DM).

Conclusions: Statins would decrease the risk of NAFLD occurrence and development of liver fibrosis in NAFLD subjects independent of accompanying DM.

Keywords: Stains; Nonalcoholic fatty liver disease; Liver fibrosis; Dyslipidemia

National Health Insurance Big Data Research: Liver Cirrhosis

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서 론

정맥류 출혈, 조절되지 않는 복수, 간신증후군 및 간성뇌증은 진행된 비대상성 간경변 환자에서 나타는 합병증으로 사망률과 간세포암종의 발생율을 높인다고 알려져 있다. 많은 선행연구에서 비대상성 간경변이 발생되는 경우 간세포암종 발생의 위험도는 매년 7~8% 증가한다고 알려져 있으며, 사망률은 매년 20~50%로 알려져 있다. 그러나 최근 의료수준의 발전에 따라 출혈, 염증으로 인한 사망률이 줄었으며 간세포암종의 진단률에도 많은 변화가 발생되었다. 무엇보다 만성 B형 간염에서 항바이러스제의 사용은 간질환의 진행과 간암 발생을 낮춘다고 알려져 있다.[1,2] 최근 항바이러스제의 광범위한 사용에 따라 만성 B형 간염 환자와 초기 간경변 환자에서 항바이러스제의 사용 후 간세포암종의 발생 및 사망률에 대한 clinical outcome이 많이 알려져 있다. 그러나 아직 비대상성 환자에서 항바이러스 사용에 따른 간세포암종의 발생 및 사망에 대한 clinical outcome에 대하여서는 알려진 바가 적다. 일부 소규모 환자를 대상으로 비대상성 환자에서 항바이러스제 사용에 따른 clinical outcome에 대한 연구가 보고되었으나 대상환자가 적고 관찰기간이 짧은 문제가 있다. 본 연구는 전국민이 단일의료보험에 속하여 있는 한국의 자료를 이용하여 항바이러스를 사용하는 비대상성 간경변환자에서 clinical outcome에 대하여 살펴보고자 하였다.

Method

Study population

연구의 분석 대상은 2007년~2014년 동안 보험기준에 따라B형 간염 항바이러스제를 최초로 처방 받은 환자 286,871명을 대상으로 하였다. 항바이러스제를 처방 받은 286,871명 중 앞선 1년 동안 항바이러스제 사용이 없고 추적관찰기간이 5년 이상 가능한 2008년~2009년에 항바이러스제를 사용한 환자를 대상으로 하였다. 연구대상기간(2008년~2009년) 동안 만성 B형 간염 환자의 보험급여 기준은 변경되지 않았으며, 급여 기준은 아래와 같았다. HBeAg(+)로서 HBV-DNA≥100,000 copies/ml이거나 또는, HBeAg(-)로서 HBV-DNA≥10,000 copies/ml인 만성활동성 B형간염 환자에서 AST(Aspartate Transaminase) 또는 ALT(Alanine Transaminase)가 80단위 이상인 환자. 만성 B형 간염의 초치료로는 lamivudine, clevudine, entecavir, tenofovir와 pegylated interferon이 가능하다.

Inclusion criteria

2007년부터 2014년까지 만성 B형 간염 환자의 보험급여 기준에 합당하여 경구용 항바이러스제를 90일 이상 사용한 사람을 대상으로 하였다. 최초 경구용 항바이러스제를 사용 한 이후 최소 5년 이상 추적관찰 자료가 있는 환자만을 대상으로 하였다. 비대상성 합병증의 정의는 조절되지 않은 복수로 입원하여 3리터 이상의 복수 천차를 받은 경우, 정맥류 출혈로 입원하여 내시경적 지혈술을 받거나 약물 치료를 받은 경우, 간성뇌증으로 입원하여 lactulose 관장을 시행한 경우, 간신 증후군으로 치료를 받은 경우로 하였다.

Exclusion criteria

항바이러스제를 사용하는 시점으로 1년 이내에 경구용 항바이러스제 (lamivudine, clevudine, adefovir, telbivudin, entecavir, tenofovir)를 사용한 병력이 있는 경우. 비대상성 합병증(조절되지 않는 복수, 정맥류 출혈, 간신증후군, 간성뇌증)이 2년 이내에 발생되었던 경우. 항바이러스제 처방 이전에 암을 진단받은 경우, 추적관찰 기간이 5년 미만인 경우를 제외하였다.

Baseline biochemical data.

분석 대상자는 비대상성 합병증이 최초 발생된 B형 간염 환자 중에서 비대상성 합병증 발생 전후 한달 이내에 보험기준에 합당하여 새롭게 항바이러스제를 사용한 경우로 한정하였다. 연구기간동안 모든 만성 B형 간염 환자에서 항바이러스제의 보험급여기준은 HBsAg 양성, 혈청 HBV-DNA PCR > 2,000 U/L, and ALT/AST >80 U/L 이상인 경우였다.

Results

1. 대상 환자 선별

2007년부터 2014년까지 항바이러스제를 보험급여로 처방 받은 286,871명 중에서 이전 비대상성 합병증 발생이 없고, 관찰기간이 5년 이상이며, 혈청 HBV-DNA PCR > 2,000 U/L, and ALT/AST >80 U/L 이상으로 새롭게 항바이러스제를 처방 받은 환자 48,365명을 대상으로 하였다 (Figure 1). 처음 항바이러스제를 투여하는 당시 대상성 간질환을 보이는 환자 45,683명과 항바이러스 투여 당시 비대상성 합병증이 동반되어 있었던 환자 2,682명을 대상으로 하였다 (Table 1). 대상자의 평균 연령은 43.5세 였으며 entecavir를 사용한 경우가 24.1%로 가장 많았으며 다음으로 lamivudine를 사용한 경우가 많았다. 항바이러스제를 처방 받은 환자의 26.9%는 관찰기간 동안 75% 이상의 복약 순응도를 보였다. 비대상성 간경변을 동반하는 경우 불응성 복수가 75.4%로 가장 많았으며, 이후 정맥류 출혈이 많았다.

2. Clinical course of compensated hepatitis B patients under NUC treatment

만성 B형 간염 및 대상성 간경변 환자에서 항바이러스제를 사용 후 첫번째 비대상성 합병증이 발생되는 빈도는 연간 1.2~2.0% 였다 (Table 2). 비대성성 합병증의 발생 빈도는 항바이러스제 사용 기간이 증가하면서 의미 있게 감소하였다 (p for trend <.0001). 5년 누적 비대상성 합병증 발생 확율은 7.4% 였다. 항바이러스제를 사용한 대상성 간질환 환자에서 간암 발생은 연간 1.7%~3.5% 였으며, hepatocellular carcinoma 발생 빈도는 항바이러스제 사용 기간이 증가하면서 의미 있게 감소하였다 (p for trend <.0001). 그러나 5년 누적 간암 발생 빈도는 11.5%로 비대상성 합병증 발생빈도 보다 높았다 (p <.0001). Compensated HBV patients에서 연간 사망율은 약 0.55~0.71% 였으며 5년 누적 사망률은 3.1%, 누적 생존율은 96.9% 였다.

3. Clinical course of compensated hepatitis B patients under NUC treatment

비대상성 간경변 환자에서 항바이러스제를 사용 후 두번째 비대상성 합병증이 발생되는 빈도는 연간 2.05~46.8% 였다(Figure 3). 비대성성 합병증의 재발 빈도는 1년 이내가 가장 높았으며 (46.8%), 항바이러스제 사용 기간이 증가하면서 의미 있게 감소하였다 (p for trend <.0001). 5년 누적 비대상성 합병증 발생 확율은 60.63%였다. 항바이러스제를 사용한 대상성 간질환 환자에서 간암 발생은 연간 1.7%~14.62%였으며, hepatocellular carcinoma 발생 빈도는 항바이러스제 사용 기간이 증가하면서 의미 있게 감소하였다 (p for trend <.0001). 비대상성 간경변 환자에서 5년 누적 간암 발생 빈도는 24.1였다. Decompensated HBV patients에서 연간 사망율은 약 2.61~19.1% 였으며 5년 누적 사망률은 32.6%, 누적 생존율은 67.4%였다.

4. Mortality according to decompensated event

비대상성 합병증의 종류에 따른 사망률을 비교하였다 (Table 3). 불응성 복수가 발생한 경우 연간 13.6%~24.3% 였으며, 첫해 사망률이 가장 높았다. 1년 사망률은 24.3%, 5년 누적사망률은 89.5% 였다. 정맥류 출혈이 발생한 경우 연간 15.1%~23.1% 였으며, 첫해 사망률이 가장 높았다. 1년 사망률은 23.1%, 5년 누적사망률은 87.0% 였다. 간신증후군이 발생한 경우 연간 10.5%~23.2% 였으며, 첫해 사망률이 가장 높았다. 1년 사망률은 23.2%, 5년 누적사망률은 92.8% 였다.

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The Liver Week 2019

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DAY 3: Saturday, June 22, 2019 (14:30-15:40)
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Common Concerns

Hapatologists and Surgeons (*K)

Chairs:
Yung Sang Lee (Univ. of Ulsan)
Sung Su Yun (Yeungnam Univ.)

Assessment of Surgical Risk in Patients with Cirrhosis

Ki Tae Yoon

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간경변증 환자에서 수술 위험성 평가

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The pathophysiology of chronic liver disease and portal hypertension predisposes the patient with cirrhosis to complications related to surgical procedures. Invasive surgery is frequently required in the patient with cirrhosis and perioperative management is challenging. Although morbidity and mortality rates correlate with progression of portal hypertension in this population, Child-Pugh classification and the MELD score can provide some prediction of risk in counseling patients and their families. A multidisciplinary approach to these patients is critical for optimizing all phases of perioperative care, including planning, preoperative evaluation, intraoperative management, and postoperative recovery. Studies of larger cohorts with matched controls and randomized controlled trials are needed to improve our understanding and management of surgical risk in cirrhotic patients.

Keywords: Liver cirrhosis, Surgery, Risk

서 론

간경변증은 만성적인 간 손상과 회복의 과정에서 발생하는 간섬유화가 진행되어 조직학적으로 섬유성 반흔에 의한 재생결절이 생기는 상태로 만성 바이러스간염, 알코올 간염 및 비알코올 간염 등이 주 원인이다. 간경변증에 대한 치료가 지속적으로 발전함에 따라 간경변증 환자의 생존률이 향상되고 이환 기간이 늘어나면서 다양한 질병에 의한 수술을 받게 되는 경우도 늘어나고 있다. 간경변증 환자는 영양 불량, 문맥고혈압, 출혈 성향, 간에서의 약물 대사 장애, 신기능 장애 및 감염의 취약성 등 다양한 요인과 관련하여 수술과 관련된 이환율과 사망률이 일반적인 경우보다 높다. 따라서 수술 시행 전 수술과 관련된 위험성을 예측할 수 있는 지표의 활용이 필요하다.

본 론

1. Child-Pugh Classification

수술 전 이환율과 사망률에 관한 평가에서 Child-Pugh 분류체계가 주로 이용되어 왔다. Child-Pugh 분류체계는 빌리루빈, 알부민, 프로트롬빈 시간, 복수 및 간성혼수의 정도에 의한 점수의 합으로 평가되고 있다. 이 분

류체계를 이용하여 간경변증 환자의 수술 후 사망률을 조사한 연구들에서 수술 후 30일 사망률을 Child-Pugh A 10%, Child-Pugh B 30%, Child-Pugh C 76~82%로 보고하고 있다. 현재 수술 전 협진에서 간경변증 환자의 수술 후 예후는 이와 같은 근거에 의하여 이루어지고 있다. 그러나 Child-Pugh 분류체계는 간경변증 환자들의 예후를 예측하는 데 있어서 몇 가지 한계점을 가지고 있다. 첫째, 5개의 구성 요소 중 복수와 간성혼수 2가지는 주관적인 요소로 객관적이지 못하며, 둘째, 모든 요소들이 가중치 없이 동일하게 취급되고 있고, 셋째, cut-off value가 통계적인 근거 없이 임의적으로 설정되었으며, 넷째, Child-Pugh 분류는 세 가지 밖에 없는데 같은 등급 내의 환자들이 균일하지 않아 같은 등급 내에서도 서로 다른 예후를 보일 수 있다는 점 등이 거론되고 있다.

2. ASA Physical Status Classification

ASA 분류체계는 1940년대 초부터 수술과 관련된 마취의 위험성 평가에 사용되어 왔다. 이 분류체계는 일정 환경에서 수술 결과와 대략적 상관관계가 있는 질병의 상태 수준을 나타내는 것으로 결과의 직접적인 예측자라기로 보다는 질병상태의 중증정도로 간주할 수 있다. ASA I은 정상, ASA II는 경증 전신질환이 있는 환자, ASA III는 중증 전신질환이 있는 환자, ASA IV는 생명을 위협하는 전신질환이 있는 환자, ASA V는 빈사상태의 환자로 수술 없이는 생존이 어렵고 수술 후에 도 사망할 가능성이 높은 환자, ASA VI는 뇌사상태의 환자로 정의된다. 이 분류체계는 다소 주관적인 평가가 이루어질 수 있는 특성으로 관찰자 간의 평가 결과 일치성이 좋지 않을 수 있는 문제가 있다. 또한 중등도 질환에 대한 분류가 없고, 경증 및 중증 질환에만 해당되는 분류만 있다. 이런 약점에도 불구하고 마취 영역에서 간경변증 환자에서 수술 위험 예측지표로 사용 및 연구되고 있다.

3. MELD Score

경경정맥 간내 문체단락술 (transjugular intrahepatic portosystemic shunt)을 시행하는 환자들의 예후를 예측하기 위해 개발된 model for endstage liver disease (MELD) 점수는 간이식 환자에서 장기 배정의 우선 순위를 결정하는 모델로 도입되었다. MELD는 혈청 빌리루빈 및 크레아티닌치와 프로트롬빈 시간의 국제표준화율 (international normalized ratio, INR)을 이용하여 계산할 수 있다. MELD 점수는 간이식을 대기하는 환자들의 단기 및 중기 사망률을 정확히 예측하는 것으로 알려져 있다. MELD 점수를 이용하여 간경변증 환자의 수술 후 사망률을 예측한 연구들이 보고된 바 있다. 수술 전 MELD 점수가 16점 미만인 환자는 16점 이상인 환자보다 수술 후 사망률이 낮았으며, 한 연구에서는 수술 후 사망률이 MELD 점수에 따라 선형 증가하는 것으로 나타났다. 140명의 수술을 받는 간경변증 환자들을 대상으로 한 연구에서 MELD 점수만이 30일 사망률을 예측할 수 있는 유일한 인자였으며 MELD 점수가 1점 올라갈 때마다 MELD 점수 5~20인 경 우에는 1%, MELD 점수 20 이상인 경우에는 2% 씩 사망률이 증가하였다. 그 외의 소규모 연구들에서도 MELD 점수가 CTP 점수에 비해 간경변증 환자들의 복강 내 수술 후 사망률을 예측하는 데 우월하다고 보고하였다. 심장 수술을 받는 간경변증 환자들을 대상으로 한 연구에서는 MELD 점수 13점 이상이 나쁜 예후와 연관이 있다고 보고되었다. MELD 점수는 간절제술을 시행하는 환자들의 예후를 예측하는 데에도 매우 유용한 것으로 알려져 있다. MELD 점수는 Child-Pugh 점수와 달리 객관적인 변수들로 이루어져 있고, 중요도에 따라 변수들에 가중치를 두고 있으며, 임의적인 cut-off value를 사용하지 않고, MELD 점수가 1점만 올라도 위험성이 비례하여 증가한다. 따라서, 최근에는 수술을 받는 간경변증 환자의 예후 판정 역시 Child-Pugh 분류보다 MELD 점수를 이용하는 추세이다. 그러나, 복수 및 정맥류 출혈과 같이 심한 문맥압 항진증을 가지고 있지만 MELD 점수 구성 요소인 빌리루빈 및 INR이 비교적 정상으로 유지되는 환자에서 MELD의 경우 수술 위험성을 충분히 반영하지 못할 수 있으며 이와 같은 경우에는 Child-Pugh 분류체계가 더 유용한 도구가 될 수 있다.

결 론

간경변증 환자들은 수술 후 이환율과 사망률이 높아 수술 전 평가에 보다 세심한 접근이 요구된다. 침습적 외과 수술이 계획된 간경변증 환자에서 위험을 예측하는 지표는 표준화되지 않았으며 전향적 연구의 시행을 통한

명확한 근거의 제시도 쉽지 않다. 그럼에도 Child-Pugh 분류체계와 MELD 점수는 환자와 보호자들의 수술 전 상담에 있어 위험한 대한 예측 정보를 제공할 수 있으며, 이러한 접근은 수술 계획, 수술 중 관리 및 수술 후 회복의 모든 단계를 최적화하는데 중요하다. 간경변증 환자에서 수술 후 위험도를 조금 더 정확히 예측할 수 있는 지표에 대한 연구는 향후 더 필요하다.

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Determination of Preoperative Liver Function and Extent of Resection

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It is necessary for the safe liver resection that the liver reserve function should be assessed accurately in the preoperative stage. There are many methods developed to assess the liver reserve using laboratory and/or radiological studies. General scoring methods such as Child-Pugh score or MELD score using a liver function tests correlates with incidence of the post-hepatectomy liver failure, however, unable to evaluate the liver reserve among the patients with low score and discriminate between normal liver and early cirrhosis. Drug clearance tests using indocyanine green (ICG) could overcome the weakness of the general scoring methods. ICG clearance tests reflects portal blood flow and the compliance of the liver. The ICG clearance test could provide credible global liver function, discriminate liver reserve between normal liver and early cirrhosis, and predict the safe range of the liver resection according to the clearance rates.

Radiological image study of the scintigraphy using 99mTc galactosyl human serum albumin (99mTc GSA) could provide liver regional function over the global liver function. Assessment of the regional liver function could be useful when the liver function is inhomogeneous, such as tumor thrombus in segmental/lobar portal vein or bile duct.

Current various methods for the assessment of the liver reserve could render the liver resection safer and expand the indication of the liver resection for the patients with borderline liver function.

Prophylaxis of Hepatitis B Virus Reactivation after Liver Transplantation

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HBV 감염에 의한 간경화 및 간세포암은 국내 전체 간이식 원인의 약 80% 를 차지하고 있으며, 이식 환자에서의 B형 간염 재발은 이식편의 소실을 유발시키고 생존율을 감소시키기 때문에 그 예방이 매우 중요하다. 간이식 후 적절한 예방요법을 시행하지 않는 경우 대체로 1개월 이내에 HBV에 재감염 되며 이로 인한 mortality rate 는 50% 이상에 달하는 것으로 알려져 있다.

1990년대 이후 HBV 재발 예방을 위해 lamivudine, adefovir, entecavir, tenofovir등의 항바이러스제와 고용량 Hepatitis B immunoglobulin (B형 간염 면역글로불린, HBIG)을 장기간 투여하는 방법이 도입되면서 HBV의 재발률이 획기적으로 감소하였으며 이식 후 생존율이 역시 큰 폭으로 향상되었다.

현재 간이식 후 HBV 감염 예방을 위해 의료기관마다 다소의 차이는 있으나 HBIG과 항바이러스제의 병용 투여가 대부분의 기관에서 예방 요법의 근간으로 자리잡았다.

그러나 HBIG 투여의 경우 비용이 많이 들고 주사로 투여해야 하기 때문에 이로 인한 불편함 및 합병증 발생 가능성이 있다. 또한 최근 도입된 항바이러스제인 entecavir, tenofovir 등의 경우 높은 효능을 보여 여러 randomized study에서 HBIG 중단 후 항바이러스제 단독 투여 시에도 기존의 병용 투여 못지 않은 예방 효과가 있음이 보고되고 있어 이에 대한 관심이 높아지고 있다.

HBIG과 항바이러스제의 병용 투여가 도입된 이후 HBIG의 사용량 감소 및 중단을 위한 여러 노력들이 이루어졌는데 anti-HBV vaccination 도 그 중 하나이다. Active immunization 을 통해 endogenous HBsAb를 형성하여 HBIG 투여 중단의 근거를 마련할 수 있다는 이론적 배경에도 불구하고 적절한 vaccination 스케줄, 면역억제 상태에서의 효과판정 기준 등은 아직까지도 확립되어 있지 않다.

Optimal Hepatitis C Virus Treatment Strategy for Patients Waiting for Liver Transplantation

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최근 경구 항바이러스제인 direct acting antiviral agents (DAAs)는 간이식 전 후 환자들에서 C형간염 바이러스(HCV)의 완치의 가능성을 크게 향상시켰다. 보다 많은 HCV 환자들이 DAAs 요법으로 완치에 도달함으로써, HCV 연관 비대상성 간경변증으로 인한 간이식 대기자들이 감소하고 있다. 그러나, 간이식 전 적절한 치료 시기, 간이식 전 HCV 제거를 통한 간기능의 회복과 간이식 대기자에서 제외(delisting), 이식편의 재감염 예방, 간이식 후 치료 시기 등과 관련하여서는 여전히 논란이 있다. 간이식 전 후 간기능 또는 콩팥기능 저하에 따른 일부 DAAs 사용의 제한과 간이식 후 투여하는 면역억제제와 DAAs 간 약물상호작용에 따른 주의가 필요하다. 또한, DAAs 치료 성적의 향상은 HCV-양성 공여자를 이용한 이식이 공여자 부족 문제를 해결하기 위한 가능한 대안으로 제시되고 있다.

Introduction

Chronic hepatitis C virus (HCV) infection-related advanced liver cirrhosis and hepatocellular carcinoma (HCC) are leading indications for liver transplantation (LT), accounting for 10% to 50% in Western countries and approximately 5% in Korea as causes of LT. However, HCV recurrence after transplantation is inevitable if it is not fully eradicated prior to transplantation. HCV reinfection can cause significant damage to the liver graft resulting in poor patient survival.

The advent of safe and highly effective, direct-acting antiviral agents (DAAs) has had great implications in the field of HCV transplantation, and changed the management of both patients on the waiting list and those with HCV graft re-infection after LT. Recent large cohort studies reported that HCV-related disease burden is decreasing in the DAA era with decreasing need for LT listing, wait-list mortality, need for LT, and post-transplant morality.[1,2] The present review discusses the optimal DAA-based hepatitis C treatment strategy for patients on the waiting for LT.

DAAs treatment in pre-LT phase

The goals for treating HCV infection before LT can be improvement of liver function to avoid liver transplantation, stabilization of liver function to reduce waitlist mortality, prevention of HCV re-infection of the graft after LT.

1. DAAs in LT candidates

DAAs should be used with caution in LT candidates with severely impaired liver function (Child-Turcotte-Pugh [CTP] class B and C) or with severe renal dysfunction (estimated glomerular filtration rate [eGFR] <30 ml/min), as both conditions may affect the metabolism of some DAAs. Sofosbuvir (SOF), ledipasvir (LDV), velpatasvir (VEL),

and daclatasvir (DCV) can be used in patients with cirrhosis without dose adjustments, regardless of liver impairment. However, the protease-inhibitor containing regimens, such as 3D (Paritaprevir/r, ombitasvir, dasabuvir), 2D (Paritaprevir/r, ombitasvir), simeprevir (SIM), grazoprevir/elbasvir (GZR/EBR), glecaprevir/pibrentasvir (GLE/PIB), sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX), can be safely used only in patients with compensated cirrhosis (CTP class A); but, they should not be recommended in patients with decompensated cirrhosis (CTP class B and C). In cases of pre-LT eGFR below 30 ml/min, SOF should be preferably planned after LT. Drug-drug interactions (DDI) between a specific DAA and any other co-administered drug, should be carefully evaluated when planning any antiviral regimen. Possible DDI should be checked on international websites (www.hep-druginteractions.org/) or discussed with a clinical pharmacologist.

2.DAA treatment in patients listed for decompensated cirrhosis

Sustained virologic response (SVR) and improvement of liver function

In the US-based SOLAR-1 trial, 108 patients with genotype 1 or 4 infection and decompensated cirrhosis (59 CTP class B and 49 CTP class C) were randomly assigned to 12 weeks or 24 weeks of the daily fixed-dose combination of LDV (90 mg)/SOF (400 mg) plus ribavirin (RBV) (initial dose of 600 mg, increased as tolerated).[3] The SVR12 rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in those who received 24 weeks of treatment. Similarly, the SVR12 rates were 86% and 87%, respectively, with 12 weeks and 24 weeks of antiviral therapy in the CTP class C patients. In the majority of participants with CTP class B or C disease, the MELD and CTP scores decreased between the baseline and post-treatment week 4. The frequency of serious adverse events increased with treatment duration in both the CTP class B group (10% week 12; 34% week 24) and the CTP class C group (26% week 12; 42% week 24). Most of the serious adverse events were related to RBV. Therapy was discontinued in 7% of CTP class B patients and 8% of CTP class C patients in the 24-week treatment arm.

In the multicenter (Europe, Canada, Australia, and New Zealand) SOLAR-2 trial, 160 genotype 1- or 4-infected patients with decompensated cirrhosis were randomly assigned to the same combination of LDV/SOF plus RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks or 24 weeks.[4] The SVR12 rate was achieved in 85% after 12 weeks of treatment (90% CTP class B, 75% CTP class C) and 90% after 24 weeks of treatment (98% CTP class B, 77% CTP class C). The baseline CTP and MELD scores were improved in the majority of patients receiving treatment; however, some participants experienced worsening hepatic function. Among non-transplanted patients whose MELD score was ≥15 at baseline, 80% (20/25) had a MELD score <15 at SVR12. Among those with a MELD score <15 at baseline, 4% (2/56) had a MELD score ≥15 at SVR12.

The ALLY-1 trial evaluated the efficacy and safety of 12 weeks of daily DCV (60 mg) and SOF (400 mg) plus RBV (600 mg with possible escalation to 1000 mg as tolerated) among patients with advanced cirrhosis (n=60, CTP class A/B/C 20%/53%/27%, G1 75%).[5] In patients with advanced cirrhosis, SVR12 rates by genotype were as follows: 82% (37/45) genotype 1, 80% (4/5) genotype 2, 83% (5/6) genotype 3, and 100% (4/4) genotype 4. The SVR12 rates by severity of cirrhosis were 92% among those with CTP class A cirrhosis, 94% among those with class B, and 56% among those with class C cirrhosis.

In a real-world study that took place in the United Kingdom, patients with decompensated cirrhosis infected with HCV genotype 1 were treated with LDV/SOF, or with DCV and SOF, for 12 weeks with or without RBV.[6] The SVR12 rates were as follows: 85% (11/13) after 12 weeks of LDV/SOF without RBV; 91% (136/149) after 12 weeks of LDV/SOF with RBV; 50% (2/4) after 12 weeks of DCV and SOF without RBV; and 88% (30/34) after 12 weeks of DCV and SOF with RBV. However, in patients with decompensated cirrhosis infected with HCV genotype 3, the SVR12 rates were as follows: 60% (3/5) after 12 weeks of DCV and SOF without RBV, and 71%

(75/105) after 12 weeks of DCV and SOF with RBV. Approximately one-third of patients saw an improvement in their MELD scores; one-third had no change; and one-third suffered deteriorating liver function 12 weeks after treatment. Improvement in the MELD score was more frequent in treated patients than in untreated patients. Longer-term follow-up of the same group of patients confirmed that treatment was clinically beneficial in patients with advanced liver disease.[7]

In the ASTRAL-4 study, 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B) were randomly assigned (1:1:1 ratio) to one of the following groups: 12 weeks of daily fixed-dose combination SOF (400 mg)/VEL (100 mg); 12 weeks of SOF/VEL plus weight-based RBV (1000 mg/d, weight <75 kg; 1200 mg/d, weight ≥75 kg); or 24 weeks of SOF/VEL[8] Among patients with genotype 1 infection, the SVR12 rates were 88%, 96%, and 92%, respectively (88%, 94% and 93% in patients with genotype 1a infection; 89%, 100% and 88% in patients with genotype 1b infection). The SVR12 rates were 100%, 100% and 75% in patients with genotype 2 infection; 50%, 85%, and 50% in patients with genotype 3 infection; 100%, 100%, and 100% in patients with genotype 4 infection. At post-treatment week 12, 47% of patients had an improvement in the CTP score, 42% had no change, and 11% had an increased CTP score. Of the patients with a baseline MELD score <15, 51% had an improved MELD score at week 12 post-treatment, 22% had no change in their MELD score, and 27% had a worse MELD score. Of the patients who had a baseline MELD score ≥15, 81% had an improved MELD score, 11% had no change in their MELD score, and 7% (2/27) had a worse MELD score. Importantly, data are almost non-existent for patients with the most advanced forms of disease (CTP score >12 or MELD score >20), who were excluded from the studies.

Effects on post-LT recurrence

The effects of pre-LT DAA treatment on post-LT recurrence were explored in a study in which 61 HCC patients with CTP class A cirrhosis were treated with SOF and RBV.[9] All patients were infected with genotype 1 or 4 and were treated for either 48 weeks or until LT. The ‘‘on treatment’’ response was very high (93% had HCV RNA less than the lower level of quantification (LLOQ) at week 4) and post-LT SVR12 was achieved in 70% of treated patients. In the same study, a ‘‘post hoc’’ analysis showed a dramatic post-LT SVR12 of 96% in the subgroup of 29 patients that had remained HCV RNA negative for at least 30 days before LT. Indeed, of the 29 patients who had HCV RNA below LLOQ for at least 30 days, only one (3%) suffered HCV recurrence after LT compared with 9 out of 14 patients (64%) with HCV RNA below LLOQ for less than 30 days. These results suggest that the removal of the infected liver, after achieving viral clearance for a minimum of 1 month, is adequate for preventing HCV recurrence after LT.

Impact on de-listing in LT candidates

Several studies assessed the impact of DAA treatment prior to LT on delisting of LT candidates. In a multicenter European real world study of patients receiving DAA treatment, 40% (41/103) were transplanted, whereas only 20% (21/103) were delisted and an additional 13% (13/103) were put on hold (inactivated) after a median period of 60 weeks.[10] The probability of being delisted was very high in patients with a MELD score <16 (about 35%) and minimal in those with a MELD score >20 (about 5%). Baseline MELD categories (MELD 16–20: HR = 0.120, *P*=0.0005; MELD >20: HR = 0.042. p <0.0001), continuous 12-week delta MELD (HR = 1.349; p <0.0001), and continuous 12-week delta albumin (HR = 0.307; *P*=0.0069) were independent predictors of inactivation on waiting list and subsequent delisting. Among patients with a MELD score <16, the probability of inactivation was 27%, 86%, and 100% in patients with 12-week delta MELD <2, 2 to 4, and >4, respectively. In contrast, in patients with a baseline MELD score ranging from 16 to 20, the probability of inactivation was 11% in patients with 12-week delta MELD <2, but 17% and 43% in patients with 12-week delta MELD of 2–4 or 4, respectively. Eventually,

among patients with a baseline MELD score >20, inactivation was observed only in 2 patients with a 12-week delta MELD >4.[10] In a similar Spanish study, 24% (29/122) of patients were delisted after DAA-based therapy.[11] No patients with a baseline MELD score >20 were delisted.

Optimal timing for pre-LT DAA treatment

To establish whether pre-LT DAA treatment is justified, the following factors should be considered: 1) The risk of death on the waiting list, which is proportional to the MELD score; 2) the possibility of clinical improvement after DAA treatment, which may favor the delisting of some patients, typically those with low MELD scores; 3) the awareness that a mild improvement in MELD score after DAA may not be enough for delisting and may work as a disadvantage for patients that lose priority on the waiting list (MELD purgatory effect in patients with high MELD score); 4) the cost-effectiveness considerations; and 5) the potential side effects as some case series show liver failure during DAA±RBV. Statements made by the European Liver and Intestine Transplant Association (ELITA) recommends the following with respect to DAA treatment in LT candidates.[12] First, patients with baseline a MELD score <16 (typically CTP class B) have a high chance (35%) of being delisted because of clinical improvement, and therefore should be treated while listed. Second, patients with baseline MELD scores between 16 and 20 (mostly CTP class C) have a chance of being delisted due to clinical improvement of about 12%. They should be started on DAAs while listed, and possible clinical improvements should be assessed after 12 weeks of therapy. Patients showing a significant improvement of MELD score >3 points and albumin >0.5 g/dl after 12 weeks on DAAs should be considered for possible delisting during the follow-up period. Third, patients with baseline MELD scores between 21 and 25 (typically advanced CTP class C) have limited MELD improvement. For these patients, a case-by-case multidisciplinary decision is advised. Fourth, patients with high MELD scores >25 are not recommended to undergo pre-LT DAA treatment; however, post-LT treatment is preferable due to their poor prognosis, significant risk of death pre- or post-LT, unknown probability of improvement, potential DAA toxicity, and rapid access to LT. A US study developed microsimulation model from LT integrated data and suggested that treating HCV before, instead of after, LT would only increase life expectancy in patients with a MELD score ≤23–27, depending on the United Network for Organ Sharing region.[13] In a recent study assessing the optimal timing of hepatitis C therapy in LT eligible patients with cost-effectiveness analysis, pre-LT treatment was reported to be cost-effective for patients without HCC with a MELD score ≤20, while antiviral treatment after LT was cost-effective in patients with a MELD score >20.[14] Overall, patients with decompensated cirrhosis and MELD score <20 on the LT waiting list should be considered for DAA treatment. However, patients with a MEDL score >20 may be less likely to see improvement and may be better to undergo transplantation than DAA treatment.

3. DAA treatment in patients listed for HCC

In patients with HCC, without cirrhosis or with compensated cirrhosis, who have an indication for LT, the ideal timing for antiviral therapy (before or after LT) remains controversial. Lower SVR rates were reported in patients with HCC treated with DAAs than in patients without HCC or in patients with HCC treated after LT (74% vs. 91% and 94%, respectively).[15] Post-LT treatment of HCV was reported to be cost-effective in patients with HCC.[14] The 1-year rate of removal from the LT waiting list due to tumor progression is estimated to be up to 10% in centers following the Milan criteria, and up to 20% in those following the extended criteria. Similarly, the risk of death from HCC recurrence after LT is as high as 10% in centers adopting the Milan criteria, and up to 20% in those adopting the extended criteria. The response to therapeutic interventions for HCC while the patient is on the waiting list further affects the prognosis either pre- or post-LT. These competing risks should be considered to avoid futile DAA treatment. This scenario is further complicated by the previous alarming reports regarding a possible increased risk of HCC recurrence after DAA treatment.[16, 17] However, prospective studies and systematic review

did not show higher risk of HCC recurrence after DAAs in patients with successfully treated HCC.[18-21] In addition, a recent study from the Italian Liver Cancer Group suggested that DAAs significantly improved overall survival when compared with no DAA treatment in patients with HCV-related cirrhosis as well as in those who underwent successful previous treatment of early HCC.[22] Thus, despite conflicting data, DAAs are considered as safe and do not increase the risk of dropout for tumor progression in patients with HCC listed for LT. According to the recommendations from ELITA statements, pre-LT DAA treatment should be restricted to those with the following features: 1) a low risk of post-transplant HCC recurrence, regardless of the model for assessing the risk (i.e. Milan criteria, alpha-fetoprotein model or other predictive models of recurrence at listing); 2) no signs of HCC progression while on HCC bridging therapy, and 3) expected waiting time >3 months.[12]

DAAs treatment in Post-transplant Phase

HCV infection can be treated post-LT either soon after the transplant, taking advantage of the removal of the infected native liver, or at the time of disease recurrence, carried out in the past. In either case, some DAAs have a limited use due to their DDI with various immunosuppressants (IS), as well as the many other drugs often prescribed to LT recipients.

1. DAAs in LT recipients

LT recipients should take life-long IS, and the possible DDI between DAAs and IS must be checked. DCV+-SOF, LDV/SOF, and SOF/VEL have no significant DDIs with any IS and antimetabolites. Regimens containing protease inhibitors, such as 2D and 3D combinations, strongly interact with all major IS. SIM strongly affects the metabolism of cyclosporine A (CsA) and, to a lesser extent, of tacrolimus (Tac) and mTOR inhibitors via CYP3A4 inhibition. A 40%-50% increase in the Tac levels is to be expected during co-administration with GZR, while a 15-fold increase in GZR AUC and a 2-fold increase in EBR AUC is expected if co-administered with CsA. A 5-fold increase in GLE AUC with higher doses (400 mg) of CSA and 9.4-fold increase in VOX AUC with CsA are expected. Therefore, SIM, GZR, EBR, and VOX should not be co-administered with CsA. Monitoring the blood levels is required when SIM, GZR, and EBR are combined with Tac or mTOR inhibitors. Two-dimensional (2D) and 3-dimensional (3D) combinations require monitoring of all major IS. GLE/PIB should not be recommended in patients requiring stable CsA doses >100 mg/day. Finally, DCV+SOF, LDV/SOF, SOF/VEL should be the preferred regimens after LT due to no or minimal DDI. Any other drug co-administered with DAAs after LT should be checked for possible DDI, such as antifungal agents, antibiotics, cardiovascular drugs, CNS drugs, recreational drugs, and even hormonal treatments.

Renal dysfunction is another common problem after LT, which limits the use of SOF. Safe and effective doses of sofosbuvir in persons with an eGFR <30 mL/min have not been established and is out of the license recommendations. However, in the TARGET 2.0 real-world cohort study, progressive deterioration of renal function and renal symptoms were reported in patients with severe renal impairment receiving a SOF-based regimen, although efficacy was comparable to that observed in patients without renal impairment.[23] Thus, SOF-free regimens should be preferred in patients with severe renal impairment. If there is no other choice beside a SOF-based regimen, close monitoring is required, and treatment should be rapidly interrupted if renal function deteriorates. Although tolerability and efficacy of GZR/EBR are satisfactory in patients with renal insufficiency, their use is not recommended after LT due to major DDI with many IS. This is also true for the 3D combination.

The issue of increased risk of rejection following HCV clearance is also a major consideration. Close monitoring of calcineurin inhibitors/mTOR is recommended, particularly at the end of DAA therapy, when the cessation of DDIs and the improved metabolic capacity of the liver may alter the exposure to various IS.

2.D AAs treatment in post-LT recurrence

SVR

In the SOLAR-1 trial, transplant recipients with HCV genotype 1 or 4 recurrence were treated with the fixed-dose combination of LDV (90mg)/SOF (400 mg) for 12 or 24 weeks with RBV.[3] The RBV dose was weight based for patients without cirrhosis or with compensated cirrhosis (1000 mg [<75 kg] to 1200 mg [= 75 kg]). For patients with CTP class B or C cirrhosis, RBV was initiated at 600 mg/d, followed by dose escalation as tolerated. In patients treated for 12 weeks with RBV, the SVR12 rates were 96% (53/55) in those without cirrhosis and 96% (25/26), 85% (22/26), and 60% (3/5) in those with CTP class A, B, and C cirrhosis, respectively. The SVR12 rates were not higher in patients treated for 24 weeks with RBV: 98% (55/56), 96% (24/25), 88% (23/26), and 75% (3/4), respectively. Similar results were reported in the SOLAR-2 study in patients with genotype 1 receiving the same treatment regimens.[4] In patients treated for 12 weeks with RBV, the SVR12 rates were 93% (42/45) in patients without cirrhosis and 100% (30/30), 95% (19/20), and 50% (1/2) in those with CTP class A, B, and C cirrhosis, respectively. In patients treated for 24 weeks, the SVR12 rates were: 100% (44/44), 96% (27/28), 100% (20/20), and 80% (4/5), respectively. Twenty-five of the 27 patients infected with genotype 4 (93%) achieved SVR12.

An observational cohort HCV-TARGET study assessed the safety and efficacy of DAA regimens in liver or kidney recipients from real-world data.[24] Among the 279 participants treated with LDV/SOF for 12 weeks or 24 weeks, the SVR rates were 97% (152/157) in those with RBV and 95% (116/122) in patients without RBV. The rate of therapy discontinuation due to an adverse event was 1.3%, highlighting the safety of the drug combination. Acute graft rejection occurred during or after cessation of therapy in 1.4% of patients, suggesting the need to monitor IS levels throughout the DAA therapy period.

The ALLY-1 trial evaluated the efficacy and safety of a 12-week course of daily DCV (60 mg) and SOF (400 mg) plus RBV (600 mg with possible escalation to 1000 mg as tolerated) among 60 patients with cirrhosis (CTP class A, B, or C) and 53 patients with HCV recurrence after LT.[5] Seventy-six percent (86/113) of participants had genotype 1 infection, including 77% (41/53) in the post-transplantation group. The SVR12 rate was 94% (50/53) among those with recurrent HCV infection post transplantation.

In another study, LT recipients with HCV recurrence were treated with the fixed-dose combination of SOF/VEL for 12 weeks without RBV.[25] The global SVR12 rate was 96% (76/79; 2 relapses). By genotype, SVR12 rates were 95% (genotype 1), 100% (genotype 2), 97% (genotype 3), and 100% (genotype 4). There was relapse in one genotype 1a patient, out of a total of 15, and one genotype 3 patient, out of 35.

In the MAGELLAN-2 trial, 80 LT recipients and 20 kidney transplant recipients without cirrhosis were treated with the 12-week course of the daily fixed-dose combination of GLE (300 mg)/PIB (120 mg).[26] All genotypes were represented, except genotype 5; 57% of participants had genotype 1 infection and 24% had genotype 3 infection. Any stable immunosuppressive regimen was allowed, except CsA >100 mg/d and prednisone >10 mg/d. SVR was achieved in 98% (98/100) of patients with no virologic breakthroughs on treatment and 1 post-treatment relapse. This regimen offers a RBV-free option for noncirrhotic liver or kidney transplant recipients. Although GLE/PIB has not been studied in transplant recipients with compensated cirrhosis, this regimen may be considered in patients who are RBV ineligible. Due to the frequency of DDIs and the need for IS dose adjustments, treatment regimens, including a protease inhibitor, are not optimal for post-LT HCV treatment. However, in LT-recipients with impaired kidney function, the combination of GLE/PIB for 12 weeks is an alternative to SOF-based regimens.

Optimal timing for DDA therapy after LT

In the IFN/RBV era, pre-emptive therapy was found to be ineffective and difficult to manage, due to severe hematological side effects and risk of rejection in the early post-LT period. Given the far better risk-benefit ratio of

DAA therapy, those principles of management can be reconsidered. The results from phase 3 studies show that excellent SVR rates can be achieved in post-transplant patients with HCV-related chronic hepatitis and compensated cirrhosis; however, the SVR rates are 10% to 30% lower in patients with decompensated cirrhosis compared with those without decompensation. Although very early DAA-based pre-emptive therapy may be an attractive option to manage HCV recurrence, no large data are currently available on the efficacy and safety of this approach. Of note, in the very early post-transplant phase, the optimal use of DAAs may be hampered by reduced postoperative liver function, impaired renal function, and DDI. At present, pre-emptive DAA therapy cannot be recommended on a routine basis. DAA treatment of HCV recurrence should be initiated early after LT, ideally as early as patients become stabilized (generally after the first 3 months post-transplant), because the SVR rates diminish in patients with advanced post-transplant liver disease.

3. HCV positive donor in DAAs era

The use of HCV-positive liver or kidney grafts in HCV-positive recipients has been encouraged by healthcare professionals, based on the fact that 5-year liver or kidney graft function is similar to that observed with organs from HCV-negative donors.[27, 28] Yet HCV-positive organs have remained under-used due to a reluctance on the part of health care professionals. Given the scarcity of donated organs and the frequency of death on the waiting list, strategies that could improve the available supply of high-quality liver grafts are severely needed. DAA regimens have proved to be highly effective to treat HCV, even in the setting of post-transplantation. The question arises as to whether transplant communities should consider the utilization of HCV-positive donors into HCV-negative recipients.[29] The transplantation from HCV-positive donors into HCV-negative recipients has both advantages and disadvantages. Advantages include increase pool of currently available donors, decrease wait-time mortality for very sick recipients (FHF, high MELD >30), potentially younger donors without other comorbidities, highly successful DAA regimens, as well as similar long-term graft and patient outcome than HCV-negative donors. Whereas, disadvantages include 100% risk of transmission of HCV for recipients, high cost of DAA, limited access to DAA regimens, requirement for preapproval by drug companies or insurance companies, possible interaction between DAA regimens and immunosuppression, as well as ethical/society barrier. The advancement in the high pan genotypic efficacy of DAA regimens may render HCV-positive liver grafts safer, extending the use of such grafts even in HCV-negative recipients, and ultimately enabling a substantial expansion of the donor pool. Recent pilot studies showed that kidney transplantation from HCV-positive donors into HCV-negative recipients, followed by the use of DAAs, can provide potentially excellent allograft function with a cure of HCV infection.[30, 31] The post-DAA era has seen increased utilization of HCV-viremic donor livers, including HCV-viremic livers into HCV-negative recipients. Early graft outcomes are similar to those of HCV-negative recipients.[32, 33] These results support the utilization of HCV-viremic organs in selected recipients, both with and without HCV infection. However, the potential to induce an infection raises ethical concerns and requires a rigorous process of obtaining informed consent from potential recipients.

Conclusions

The recent advent of DAAs has dramatically increased the chances of curative treatment for the transplant population. As more HCV patients achieve cure with DAA regimens, the rate of LT wait-listing for HCV complicated by decompensated cirrhosis has already been on a decline. However, the timing for treatment of the infection remains controversial; the question remains, whether to pursue HCV eradication before LT to improve liver function, delist some patients and prevent graft infection, or whether to pursue treatment as early as possible after LT, rather than waiting for hepatitis C recurrence. Patients with decompensated cirrhosis and MELD score <20 on the LT

waiting list should be considered for DAA treatment. However, patients with MEDL score >20 may be less likely to improve and might be better served by transplantation than DAA treatment. DAA treatment of HCV recurrence should be initiated early after LT, ideally as early as possible when the patient is stabilized. DAAs should be used with caution in LT candidates or recipients with severely impaired liver function (CTP class B and C) or with severe renal dysfunction (eGFR <30 ml/min), as both conditions may affect the metabolism of some DAAs. In LT recipients, the potential DDI between DAAs and IS should also be verified. Moreover, in the DAA era, the use of HCV-positive donors may represent a potential approach to safely expanding the donor pool.

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The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 3: Saturday, June 22, 2019 (09:00-10:00)
ROOM D [2F] 205

KAHBPS-KLTS-KLCA Joint Symposium 1

Unresolved Issues in HCC: Medical and Interventional Radiology

Chairs:

Yun Hwan Kim (Korea Univ.)
Jaeseok Hwang (Keimyung Univ.)

Adjuvant Therapy after Curative Treatment: Enough or Still Lacking?

Su Jong Yu, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Yoon Jun Kim, Jung-Hwan Yoon

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

Hepatocellular carcinoma (HCC) is a common malignancy in the world. Although resection and various loco-regional therapies can achieve eradication or complete ablation of early stage HCC, HCC recurrence after curative treatments is still common. Although candidates for medical ablation usually exhibit compensated hepatic functional status, the frequent recurrence of HCC after successful ablation contributes to short survival. Therefore, attempts to prevent HCC recurrence are essential to prolong survival. Efforts in preventing HCC recurrence after curative therapies include prevention of early recurrence by improving liver immunity and eliminating microscopic tumor foci or micro-metastases, and prevention of late recurrence from multi-centric carcinogenesis by reducing the hepatitis activity and using antiviral therapies based on viral suppression/eradication. However, sorafenib, a tyrosine kinase inhibitor, was not an effective intervention in the adjuvant setting for HCC following resection or ablation in a phase 3, double-blind, placebo-controlled study (STORM). In recent clinical trials, adjuvant cytokine-induced killer (CIK) cell-based immunotherapy increased progression free- and overall survival after curative treatment of HCC. More recently, phase 3 randomized placebo controlled clinical trials to examine the recurrence-preventing effect of immunotherapies including immune checkpoint inhibitors (ICIs) after curative treatment in patients with HCC who are at high risk of recurrence after curative hepatic resection or ablation are in progress (nivolumab, NCT03383458; durvalumab monotherapy or in combination with bevacizumab, NCT03847428; and pembrolizumab, NCT03867084). Treatments to prevent recurrence as well as early detection and early curative treatment are extremely important to improve the prognosis of patients with HCC. Thus, further research on this issue should be carried out.

Direct Acting Antiviral and HCC in Chronic Hepatitis C: Friend or Foe?

Hyung Joon Kim

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만성 C형 간염에서 직접 작용 항바이러스약제와 간세포암종 : 친구 혹은 적?

김 형 준

중앙대학교병원 내과학교실

Introduction

Although several robust scientific evidences sustain the benefic role of SVR after interferon therapy in the natural history of cirrhosis with a decreased incidence of Hepatocellular Carcinoma (HCC), currently a hot debate about the impact of DAAs on HCC development animates the scientific community. In spring 2016 this topic became particularly hot for the publication of two papers suggesting a potential increase of HCC occurrence and recurrence rates in patients undergoing DAA schedules. In addition to DAAs not offering IFN''s direct antiproliferative property, it was hypothesized that DAAs may also adversely impact immune surveillance, resulting in higher HCC risk.Since those publications, more than 100 papers, letters or communications have been published until now. The purpose of this review is to describe the interaction between DAA therapy for HCV and HCC incidence, HCC recurrence, and DAA efficacy.

Risk of Incident de novo Hepatocellular Carcinoma After Direct-Acting Antiviral Agent Treatment

In studies included more than 30,000 HCV patients, overall, SVR resulted in an approximately 70% reduction in HCC risk; this effect was evident early (within 3–-6 months) and increased over time. Patients who were treated but failed to achieve SVR with DAA remained at high risk for HCC. The relative benet of SVR persisted after accounting for demographic and clinical differences between patients approximately 70% reduction in HCC risk; this effect was evident early (within 3–-6 months) and increased over time. Patients who were treated but failed to achieve SVR with DAA remained at high risk for HCC.

In a retrospective cohort study of more than 60,000 US Department of Veterans Affairs (VA) patients with chronic HCV, DAA recipients tended to be older than IFN recipients, were more likely to have cirrhosis, and were more likely to have comorbid conditions, such as diabetes and alcohol abuse, that elevate the risk for HCC.7 After adjusting for these confounders in multivariate analysis, the risks for HCC after DAA and IFN treatments were no different (adjusted hazard ratio [aHR], 1.12; 95% CI, 0.95-1.32). Other studies comparing DAA- and IFN-treated patients have come to similar conclusions. Large cohort studies also confirm that patients with DAA-induced SVR have a significantly lower risk for HCC compared with treatment failure or no treatment. A study of more than 20,000 VA patients found that DAA recipients who achieved SVR had a more than 70% lower risk for HCC

compared with nonresponders (aHR, 0.28; 95% CI, 0.22-0.36).

Risk of Hepatocellular Carcinoma Recurrence After Direct-Acting Antiviral Agent Treatment

Meta-analyses show that IFN-based antiviral therapy after curative HCC treatment reduces the likelihood of cancer recurrence and improves survival. Although data have demonstrated decreased risk of incident HCC after DAA therapy in patients with HCV cirrhosis, there continues to be debate about the risk and aggressiveness of HCC recurrence after DAA therapy in patients with a history of HCC. The first such study included 58 patients with previously treated HCC, of whom 16 (27.8%) experienced recurrent tumor after a median follow-up of 6 months from DAA initiation. A simultaneous publication reported HCC recurrence in 17/59 patients (28.8%). These recurrence rates were alarmingly high compared with historic controls, and some recurrences appeared to be temporally associated with DAA exposure. The available data are conflicting, and the published studies show different and relevant methodological limitations: heterogenous cohorts, potential misclassification of HCC, the absence of an adequate control group, short follow-up time and different length of follow-up . There are no conclusive data that DAA therapy is associated with increased or decreased risk, differential time to recurrence, or aggressiveness of recurrent HCC in patients with complete response to HCC therapy

Timing of Direct-Acting Antiviral Agent Treatment After Hepatocellular Carcinoma Complete Response

One of the most consistent correlates for early recurrence is the interval between HCC complete response and DAA initiation, with shorter intervals being associated with higher risk of recurrence. Reig and colleagues34 found higher recurrence (41% vs 23%) in patients treated within 4 months of HCC complete response. DAA therapy should not be withheld from patients with complete response to HCC therapy; however, DAA therapy can be deferred 4–-6 months to confirm response to HCC therapy. Patients with complete response to HCC therapy who are treated with DAAs have a continued risk of HCC recurrence and require HCC surveillance, which should be conducted indenitely with dynamic contrastenhanced computed tomography or magnetic resonance imaging every 3–-6 months.

Conclusion

DAAs dramatically enhanced our ability to cure chronic HCV and prevent its downstream complications. Several large cohort studies demonstrate that DAA-induced SVR reduces the risk for de novo HCC. However, the residual risk for HCC after SVR means that surveillance is still required for patients with advanced fibrosis and cirrhosis. Additional well-designed studies are needed to determine the consequences of DAA therapy in patients with previously treated HCC, although the initial concern that DAAs increase recurrence risk has generally not been borne out in subsequent studies.

How to Overcome Long-Term Decline in Survival of HCC Patients Treated with Ablation

Shuichiro Shiina

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Image-guided percutaneous ablation is considered best in the treatment of early-stage hepatocellular carcinoma (HCC). Ablation is potentially curative, minimally invasive, and easily repeatable for recurrence. In our early study, we performed 2,982 RFA treatments on 1,170 primary HCC patients and the 1-, 3-, 5-, 7-, and 10-year survival rates of all 1,170 HCC patients were 96.6%, 80.5%, 60.2%, 45.1%, and 27.3%, respectively (Shiina S, et al. Am J Gastroenterol 2012). Multivariate analysis demonstrated that age, anti-HCV, Child-Pugh class, tumor size, tumor number, serum DCP, and serum AFP-L3 were significantly related to survival. A recent nationwide survey in Japan showed long-term survivals were similar between surgical resection and RFA. A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small HCC (SURF trial) recently demonstrated that the 3-year RFS of patients underwent surgery and RFA was 49.8%, 47.7%, respectively (hazard ration [HR] 0.96, 95% CI 0.72-1.28; *P*=0.793).

It is true that survival of HCC patients declines gradually after ablation. Even in small HCC, survival becomes lower in the long run. However, this is not specific to ablation. The situation is almost the same in surgical resection. In liver cancer, a survival declines considerably even after 5 years while in stomach cancer, colorectal cancer and many other cancers, recurrence and death are rare after 5 years. According to the cancer survival rates at Japanese Association of Clinical Cancer Centers, in liver cancer, 5-, and 10- year survival rates were 32.2%, and 15.3%, respectively while in stomach cancer, they were 70.9%, and 69.0%, respectively and in colorectal cancer, they were 72.1%, and 69.8%, respectively.

There are two main reasons why the survival declines. One is frequent recurrence of HCC. It is due to micro-metastasis, metachronous multicentric carcinogenesis, and local tumor progression. The other is gradual deterioration of liver function. It is due to loss of liver tissue by treatments and advance of underlying liver cirrhosis.

In order to overcome the long-term decline in survival, to improve outcomes of ablation is most important. Various innovations have been introduced in the field of ablation, such as a dedicated US transducer for puncture, a dedicated procedure bed, multimodality fusion imaging and US contrast agents. New-generation MWA systems incorporating antenna cooling and high-power generation have been receiving considerable attention. New-generation MWA can create a more predictable ablation zone, a larger ablation volume in a shorter procedure time. However, MWA antenna has some problems; it is difficult to insert into the liver. It cannot be seen clearly by US. It is easily broken. Further studies are needed from viewpoints of adverse events and long-term survival.

Incidentally, ablation is highly operator-dependent. Its skills and outcomes are very different from operator to operator. In order to disseminate skills and know-hows for ablation, we have held domestic training programs 12 times, with a total of 201 participants. We also have held international training programs six times, which were successfully completed with 91 participants in total. Programs are composed of comprehensive lectures, live demonstrations and case studies. In the live demonstrations, RFA and new-generation MWA are performed on a

wide variety of cases. In the case studies, difficult to ablate cases from participants' hospitals are presented and discussed. Our programs may be useful to provide opportunities to understand basic concepts and learn essential technical tips in ablation.

Sophisticated ablation, which is potentially curative, minimally invasive and easily repeatable for recurrence, would be superior to conventional surgery in some selected cases.

Another important way to improve long-term outcomes in HCC is to treat underlying liver disease. It may suppress recurrence of HCC and prevent deterioration of liver function. In our institution, the B-HCC prognosis improved dramatically ($P<0.001$) over time, whereas the prognosis of C-HCC improved moderately ($P=0.01$). The difference in antiviral therapy feasibility may explain the difference in the survival improvement in the two groups. Compared with NA, which can be administrated even to B-HCC patients with impaired hepatic function without serious adverse effects, IFN-based therapies were associated with a higher adverse effect rate and a lower SVR rate, especially with advanced liver fibrosis. Incidentally, the 5-year survival rate of C-HCC patients treated with IFN-based therapy during HCC treatment was actually 87.1% in our institution. Introduction of direct acting antivirals (DAA) results in sustained virological response (SVR) rates of >90% in treated patients whatever the stage of liver fibrosis with an excellent safety profile. In the era of DAA which can eradicate HCV in more than 90% of patients, the C-HCC prognosis will improve significantly.

DAY 3: Saturday, June 22, 2019 (10:20-11:20)
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KAHBPS-KLTS-KLCA Joint Symposium 2

Unresolved Issues in HCC: Surgical and Radiation Oncology

Chairs:

Hee Jung Wang (Ajou Univ.)
Jinsil Seong (Yonsei Univ.)

Will Laparoscopic Approach Be Almighty Weapon in Surgery of HCC?

Jong Man Kim

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Introduction

Liver resection is an excellent treatment option for selected patients with hepatocellular carcinoma (HCC). Open compared with laparoscopic surgery has been considered as being "more suitable" for liver resections. Additionally, the concern of excessive bleeding during laparoscopic liver resection (LLR), attributed to the inability to apply manual compression of bleeding vessels, was also invalidated. Two international LLR consensus conferences convened, the first in Louisville, Kentucky in 2008,11 and the second in Morioka, Japan in 2014.12 The first conference stated that minor LLRs are safe and should be a standard practice. Second conference showed not only noninferiority of LLR compared with open liver resection (OLR) but also superiority of LLR in several parameters

Outcomes in HCC

There is critical to demonstrate that LLR is at least noninferior to OLR in oncologic outcomes. Previous most reports in the literature show comparable overall survival (OS) and disease-free survival (DFS) rates between LLR and OLR. Not only was LLR established as an oncologically noninferior operation compared with OLR but also some investigators demonstrated superior results with LLR. The investigators attributed these results, favoring LLR over OLR, to two factors: first, less blood loss in the LLR group; blood loss is known to be a risk factor for HCC recurrence. Second, in contrast to significant mobilization and tissue manipulation before and during parenchymal transection for the OLR, the laparoscopic resections were performed using the anterior approach, with parenchymal transection taking place before any significant mobilization. Thus, a no touch technique is performed, which may be associated with improved oncologic outcomes.

Resections in cirrhotic patients

Liver resections in cirrhotic patients are associated with a relatively high hospital mortality of 1% to 4%, even at high-volume centers. Therefore, LLR in cirrhotic patients is conceptually perceived as being risky, and in many centers, Child–Pugh B patients are precluded from laparoscopic resections.

HCC in difficulty segments

HCC in the posterior-superior liver is considered as difficult and inaccessible parts for LLR. Recent study reported that LLR was associated with less blood loss and shorter hospital stay. There were no statistically significant differences between the 2 groups in operative time, postoperative complications, rate of negative resection margins, and the 3-year OS and DFS rates.

Conclusion

Comparable oncologic outcomes (R0 rate, 5-year DFS, and 5-year OS) have been reported for LLR for HCC compared with OLR using case controls, propensity score matching, and meta-analyses. Further studies will need to define which patients with advance cirrhosis or HCC in the difficult area are suitable for an laparoscopic approach.

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Priority Policy for Patients with HCC Awaiting Liver Transplantation: Unresolved Issue?

Dorry L. Segev

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Historically, exception points for hepatocellular carcinoma (HCC) in the United States led to higher transplant rates and lower waitlist mortality for HCC candidates compared to non-HCC candidates. As of October 2015, according to changes in US policy, HCC candidates must wait 6 months after initial application to obtain exception points. We have studied 2013-2017 SRTR data. Based on this, we identified 39 350 adult, first-time, active waitlist candidates and compared deceased donor liver transplant (DDLT) rates and waitlist mortality/dropout for HCC versus non-HCC candidates before (October 8, 2013-October 7, 2015, prepolicy) and after (October 8, 2015-October 7, 2017, post-policy) the policy change using Cox and competing risks regression, respectively. Compared to non-HCC candidates with the same calculated MELD, HCC candidates had a 3.6-fold higher rate of DDLT prepolicy (aHR = 3.49 3.69 3.89) and a 2.2-fold higher rate of DDLT postpolicy (aHR = 2.09 2.21 2.34). Compared to non-HCC candidates with the same allocation priority, HCC candidates had a 37% lower risk of waitlist mortality/dropout prepolicy (asHR = 0.54 0.63 0.73) and a comparable risk of mortality/dropout postpolicy (asHR = 0.81 0.95 1.11). Following the policy change in the United States, the DDLT advantage for HCC candidates remained, albeit dramatically attenuated, without any substantial increase in waitlist mortality/dropout. In the context of sickest-first liver allocation, the revised policy seems to have established allocation equity for HCC and non-HCC candidates.

Radiation Therapy for Early HCC: Will It Be a Good Option in Practice?

Sang Min Yoon

Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Currently recommended curative treatment options for hepatocellular carcinoma (HCC) include hepatic resection, liver transplantation, and percutaneous ablative therapies. However, these treatments can only be applied to the limited groups of patients according to baseline hepatic function, availability of organs, and tumor location. Therefore, alternative non-invasive local treatments should be considered in such cases.

With remarkable recent advances in radiation therapy techniques, including four-dimensional computed tomography, intensity-modulated radiation therapy, image-guided radiation therapy, and controlling respiratory movements during radiation therapy, stereotactic body radiation therapy (SBRT) has been regarded as a good alternative treatment option for early HCCs that are not suitable for curative treatments. Many prospective and retrospective studies have evaluated the ablative role and safety of SBRT for small HCCs and showed that SBRT results in an excellent local tumor control and minimal treatment-related toxicity.

Here, we summarize recent updates and discuss the future perspectives of the role of SBRT for early HCC.

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 3: Saturday, June 22, 2019 (14:20-15:40)
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Asian Forum

Korea-Japan-Taiwan

Chairs:
Jin Mo Yang (Korea)
Tetsuo Takehara (Japan)
Jia-Horng Kao (Taiwan)

Current Status and Emerging Issues in Liver Diseases in Japan

Hayato Hikita

Department Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan

The introduction of direct-acting antivirals (DAAs) substantially increased the rate of sustained virologic response. In Japan, IFN-free DAA (Direct acting antiviral) treatment has been introduced in 2014. First IFN-free DAA treatment is asunaprevir (ASV);an NS3/4A inhibitor +daclatasvir (DCV); an NS5A inhibitor. After that, many IFN-free DAA treatments were approved until now. For patient with HCV genotype 1, which is a major HCV genotype in Japan, ASV+DCV, ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) and ASV/DCV/beclabuvir (BCV) were used, and ledipasvir(LDV)/sofosbuvir(SOF), grazoprevir (GZR)+Elbasvir (EBR) and glecaprevir (GLE)/pibrentasvir (PIB) are used. Nowadays, SVR rates of any IFN-free DAA treatments exceed 95%. However, resistance-associated substitutions (RASs) emerge in patients with virologic failure (VF) after IFN-free DAA treatment to create a new issue. Since an NS5A inhibitor is a key drug for IFN-free DAA treatment and RASs generated by a NS5A inhibitor show cross resistance to other NS5A inhibitors, we should pay attention NS5A RASs, especially, after VF.

To examine emerging RASs, we deep sequenced HCV and compare HCV RASs between before and after VF. We treated 322 and 1258 hepatitis C patients with ASV+DCV or LDV/SOF, respectively. With ASV+DCV treatment, 19 (5.9%) patients experienced VF including 4 NR (non-response), 8 BT (break through) and 10 relapses. Among them, 14 patients' HCV RASs could be analyzed at both time point before and after treatment. All 14 patients infected with HCV genotype 1b and did not receive any NS5A inhibitors before ASV+DCV treatment. Although some patients carried HCV with L31M/V-Y93H RASs at baseline as a minor cone, but no patients carried HCV withL31M/V-Y93H RASs as a major clone. In contrast, HCV with L31M/V-Y93H RASs was detected as a major clone in 13 patients at the time of VF. The other 1 patient carried HCV with P32del at the time of VF, which was not detected at baseline. The HCV with P32del was also detected as a major clone post 24 weeks after treatment. With SOF/LDV, 13 (1.0%) patients experienced VF including 3 NR and 10 relapses. Among them, 9 patients' HCV RASs could be analyzed at both time point before and after treatment. All 9 patients infected with HCV genotype 1b and did not receive any NS5A inhibitors before SOF/LDV treatment. One patient did not carry a signature RAS at the L31 or Y93 position at baseline but Y93H was found at the time of VF. Among the other 9 patients, 5 had HCV with L31V/F-Y93H, 3 had HCV with Y93H, and 1 had HCV with L31M at baseline. All 8 patients who were positive for baseline Y93H either harbored this substitution at a high frequency before treatment or exhibited an increase in frequency after treatment. One patient who carried HCV with L31M at baseline developed HCV with P32del at the time of VF; the P32del was not detected at baseline. The P32del HCV was detected as a major clone for more than a year after VF.

Among the VF patients with sequenced HCV after treatment with ASV+DCV or SOF/LDV, 4 patients carrying HCV with L31V/F-Y93H or Y93H were re-treated with GLE/PIB, and all of them achieved SVR. On the other hand, in the phase III trial of GLE/PIB in Japan, 2 of 33 DAA-treated patients had the P32del mutation before treatment, and the treatment was not effective in both cases. Effective treatment was not established for patients carrying HCV with P32del. So we next examined treatment options for chronic hepatitis C patients carrying HCV

with P32del using humanized liver chimeric mice.

After inoculation of sera from the patient carrying HCV with P32del after SOF/LDV treatment or DAA-naïve patient carrying wild-type HCV without any RASs at L31, P32 or Y93 into chimeric mice, serum HCV RNA levels increased and developed persistent HCV infection in both inoculated mice. Two-week NS5A inhibitor (LDV, EBR) monotherapy decreased serum HCV RNA levels to undetectable levels in mice infected with wild-type HCV, but not at all in mice infected with P32del HCV. Three-week IFN monotherapy decreased serum HCV RNA levels by 2.8±0.2 log IU/ml from baseline in mice infected with wild-type HCV as same as those in mice infected with P32del HCV. To examine the efficacy of a combination therapy, mice in each group were divided into three treatment groups. One group received 3 weeks of LDV+GS-558093 (a NS5B inhibitor), another group received 3 weeks of simeprevir(SMV)+GS-558093 treatment, the other group received 3 weeks of SMV+pegIFN. In mice infected with wild-type HCV, all three combination therapies rapidly deceased serum HCV RNA levels to below the sensitivity. In contrast, in mice infected with P32del HCV, LDV+GS-558093 reduced serum HCV RNA levels only by 1.0±0.5 log IU/ml from baseline. SMV+GS-558093 reduced serum HCV RNA levels by 3.0±0.4 log IU/ml from baseline and SMV+pegIFN reduced serum HCV RNA levels to below the sensitivity. Combination therapy with an NS3/4A protease inhibitor and a nucleotide NS5B inhibitor or pegIFN alfa-2b may be a treatment option for HCV-infected patients with P32del.

Current Status and Emerging Issues in Liver Diseases in Taiwan

Chun-Jen Liu

Department of Internal Medicine, Graduate Institute of Clinical Medicine and Hepatitis Research Center; National Taiwan University College of Medicine and Hospital, Taiwan

Hepatitis B virus (HBV) infection and related liver diseases are a heavy disease burden worldwide, particularly in Asia-Pacific region. Thus, Taiwan has been fighting this virus since the late 1970s, and successful results have been achieved. Currently, the HBsAg carriage rate drops to below 1% in the young generation after implementation of nationwide vaccination program. After 15-year active treatment of patients with CHB through government reimbursement of peg-interferon and oral nucleos(t)ide analogue(NUC), incidence of HBV-related morbidity and mortality was documented to be decreased gradually.

The World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis since 2016 (Chen DS, 2019). The Taiwanese people and government follow the strategy and make great efforts towards the elimination of chronic hepatitis C. Efforts from experts, public health officers, legislators, and the government leaders have culminated in a consensus of reaching the WHO goals in 2025—ie, 5 years earlier than the 2030 deadline set by WHO. Accordingly, the Taiwan Hepatitis C Policy Guideline 2018–20256 was approved and published at the beginning of 2019. The government will provide US$1·7 billion in the coming 8 years for the control of hepatitis C. Actions will include lowering the barriers of access to care, screening strategies, continuum of care, preventive measures for high-risk populations, improving liver health literacy on the prevention of new infections and reinfections, liver disease management, outcome evaluation of policy and interventions, and innovation, research, and development.

Non-alcoholic fatty liver disease (NAFLD) is an emerging disease burden in Taiwan accompanying westernization of lifestyle and food. The prevalence of fatty liver is increasing; however definite prevalence or number of patients suffering from severe form of NAFLD such as steatohepatitis and cirrhosis is still lacking in Taiwan. Moreover, there is no approved medication for the treatment of NAFLD. Lifestyle modification and control of metabolic derangement remain the key strategies for the management of NAFLD.

Reference

1. Chen DS. Taiwan commits to eliminating hepatitis C in 2025. Lancet Infect Dis 2019; 19:466-467.

Current Status and Emerging Issues in Liver Diseases in Korea

Yoon Jun Kim

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

There are several issues raised recently in the hepatology field in Korea. Wide use of nucleos(t)ide analogues brings rapid decrease of decompensated patients due to chronic hepatitis B virus (HBV) infection. On the other hand, the crude incidence of primary liver cancer associated with HBV infection has been increased during recent decades in Korea. Elimination program of hepatitis C virus (HCV) was initiated with massive use of direct antiviral agents. However, active screening for hidden HCV infection is important for HCV elimination. Nonalcoholic fatty liver disease (NAFLD) has become prevalent in Korea in the last decade. The Korean society needs to quickly control the increasing prevalence of NAFLD and reduce its complications. Vaccination for hepatitis A virus (HAV) has been implemented as one of the national vaccination programs despite the epidemiological transition of HAV in Korea. Recent epidemic of HAV warns the effectiveness of the program. These topics will be discussed in the lecture.

Cirrhotic Portal Hypertension: From Arterial Vasodilatation to Systemic Inflammation

Han-Chieh Lin

Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital and, National Yang-Ming University, Taiwan

Chronic liver injury will eventually lead to development of cirrhosis. Increased intrahepatic resistance due to distorted liver structure during hepatic fibrosis is the initial trigger for the development of cirrhotic portal hypertension. The classical hemodynamic derangement in cirrhotic portal hypertension included peripheral and splanchnic arterial vasodilatation with the development of hyperdynamic circulation that is characterized by increased cardiac output and decreased peripheral and splanchnic arterial resistances. Previous studies have shown that, following the development of portal hypertension, intestinal bacterial translocation occurred. This phenomenon would lead to the development of systemic inflammatory response. In addition, the bacterial translocation associated endotoxemia will further exacerbate the hyperdynamic circulatory derangements with increased in intrahepatic resistance. A number of studies have shown that increased plasma endotoxin level following bacterial translocation in cirrhosis with portal hypertension play in part a role for the pathogenesis of cirrhotic cardiomyopathy, hepatopulmonary syndrome, kidney injury, and encephalopathy. It is also known that systemic inflammation is a hallmark of acute on chronic liver failure. Currently, there is no specific treatment to block bacterial translocation. The role of long-term antibiotic prophylaxis is still under debate. Fecal microbiome transplantation has shown some potential beneficial effects, but its long-term outcome is not known. It is now recognized that cirrhotic portal hypertension may be regarded as a systemic inflammatory multi-organ syndrome.

DAY 3: Saturday, June 22, 2019 (09:00-10:00)
ROOM A [2F] 201-202

USG Session 1

Upgrading the USG Education (*K)

Chair:
Soon Koo Baik (Yonsei Univ. Wonju)

Current Status of Ultrasonography Education Program and Ultrasonography Specialist Certificates of KASL

Hyung Joon Yim

Division of Gastroenterology, Department of Internal Medicine, Korea University Medical College, Seoul, Korea

As abdominal ultrasonography help physician to visualize the organs and structures in the abdomen, it became one of basic and essential initial evaluation tools of abdomen currently. As of 2019, upper and lower abdominal ultrasonography can be reimbursed to health insurance system. In addition, resident of Internal Medicine should learn ultrasonography and get proper training for applying the Board Certified Internal Medicine Specialist.

With this regard, Korean Association for the Study of the Liver (KASL) launched "the Quality Management Committee of Abdominal Ultrasonography" in 2018. The committee is responsible for qualification of internists performing abdominal ultrasonography and issuing the certificate of abdominal ultrasonography subspecialist. For getting the certificate, experience of 200 cases of abdominal sonography and 9 points of educational credits are mandatory. Among the 9 points, 4 points should be obtained from the ultrasonography educational session sponsored by KASL. Last year, 20 doctors obtained the certificate. KASL will receive the application for the upper abdominal ultrasonography subspecialist in September this year. All the applying documents should be submitted to the electronic management system of the KASL website.

The Korean Association of Internal Medicine indorsed the Korean Association of Clinical Ultrasound and the Korean Society of Gastroenterology for the education of abdominal ultrasonography trainer. KASL approves the qualification for abdominal ultrasonography trainer together with the Korean Society of Gastroenterology. For obtain the qualification for abdominal ultrasonography trainer, 9 points of educational credits are also needed. Experiences as a speaker or a chair at ultrasonography session of academic meeting are also required in addition to 200 cases of abdominal sonography practice. Last year, a total of 78 doctors obtained the certificate. In addition, 9 doctors applied to the certificate this year.

Currently, KASL opens ultrasonography educational sessions at the Liver week and the Korean Digestive Diseases Week. In the other hands, 3 times of hands-on workshops are held separately.

Residents of Internal Medicine can learn basic skills of performing abdominal ultrasonography through class room lectures and hands-on practice workshops. Three hour education can replace the experience of abdominal sonography of 17 patients.

In conclusion, this ultrasonography sessions are planned to educate the ultrasonography and to issue the educational credits, eventually for the better qualification of knowledge and technique of ultrasonography for members of KASL and trainees. KASL is making every effort to provide more opportunity for better ultrasonography education.

References

1. http://www.kasl.org/license/expert/?sn=2&sn2=1.

How Do I Teach Abdominal USG for Trainee?

Yun Soo Kim

Department of Gastroenterology and Hepatology, Gil Medical Center, Gachon University, Incheon, Korea

Learning Abd USG for Physician:

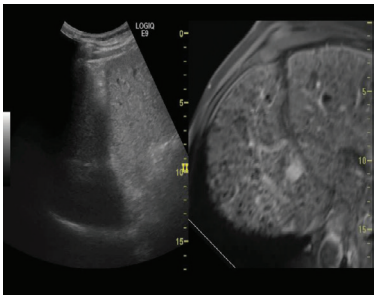
How Did I Learn Abd USG ?
- My Experience

Why Trainees Feel Difficult ?

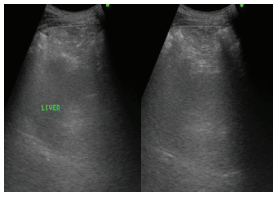
Indirect Image

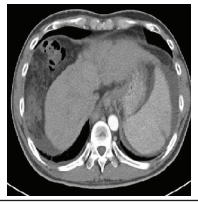
Changing Orientation (Direction)

Obstacles for scanning: artifacts, poor sonic window,...



Understanding Limitation of USG





Trainees;

Medical students

Medical Residents

Clinical Fellows

How Do I Teach Abd USG for Trainee

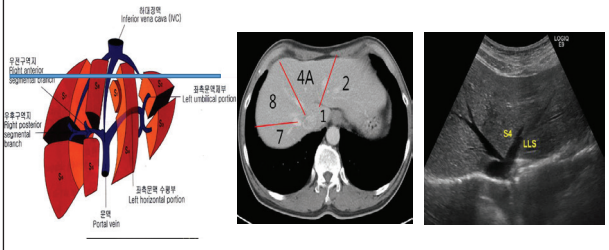
Lecture : Liver, Bilary & Pancreas

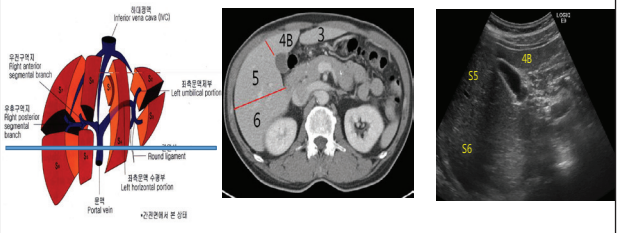
모식도(scan level), CT 와 USG image 비교

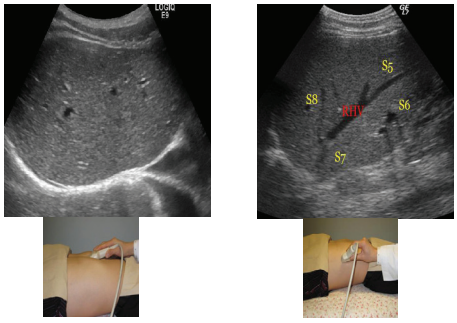
Hands-on: standard images

Pathologic conditions

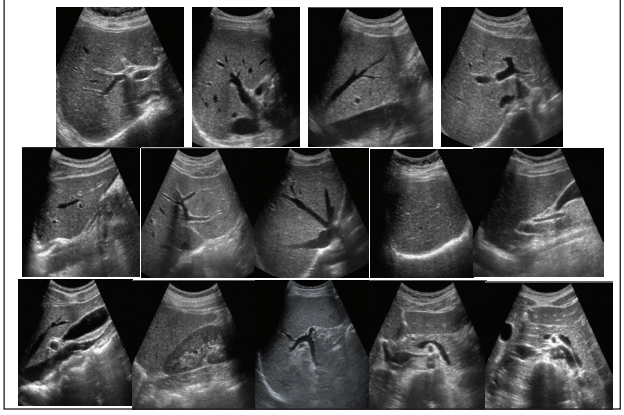
모식도 – CT – USG







Standard USG Images



Hands-on

Normal: junior residents
scan techniques

Patients: senior residents, fellows

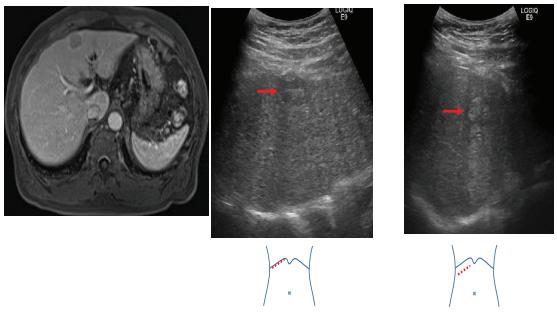
clinical correlation

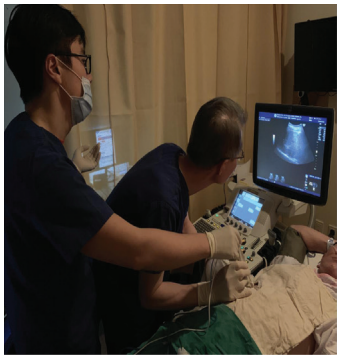
병변을 miss하였을때 CT 나 MR을 이용한 self-learning

CEUS

procedures: biopsy, abscess drainage, RFA

Scan 위치에 따른 초음파 image 차이





Instruments, Physics

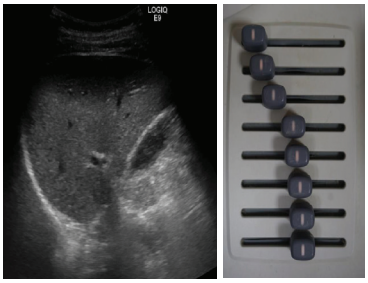
Gain

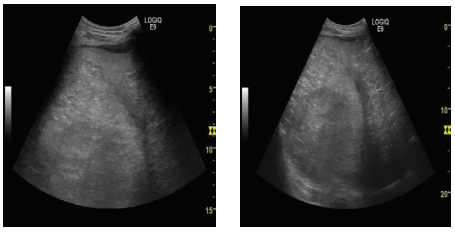
TGC

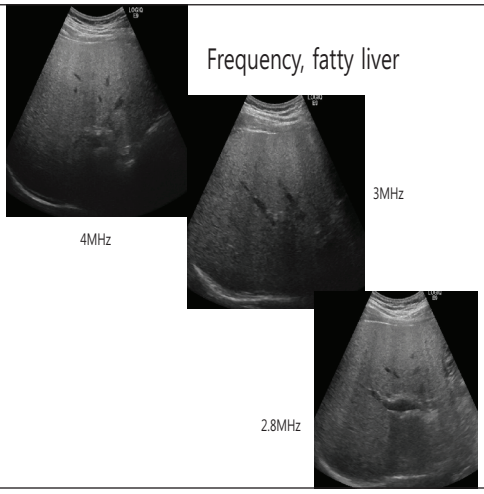
Depth

Focus

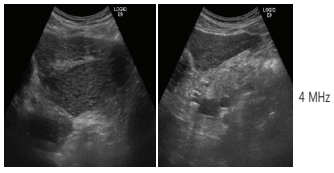
Frequency, probe

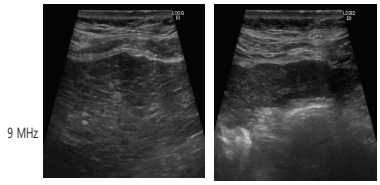




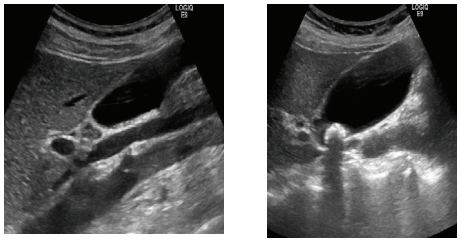


Frequency
- LC, liver surface





Praise Dances Whale !!!
- Trainee, 아낌 없는 칭찬과 격려가 필요 !!!



How to Perform Contrast-Enhanced USG: Experiences in Japan

Fuminori Moriyasu

Center for Cancer Ablation Therapy, Sanno Hospital, Tokyo, Japan

Ablation therapy for liver and pancreatic cancer is performed under ultrasound imaging guidance. Contrast-enhanced ultrasound (CEUS) is used for tumor delineation and efficacy evaluation in local ablation therapy. Sonazoid gives us long lasting Kupffer phase imaging in which bubble signals are emitted from Kupffer cells after phagocytosis. Vascular phase imaging is used for differential diagnosis of the tumor and Kupffer phase imaging is used for delineation of the tumor and ablation area.

At the same time, ultrasound fusion imaging with CT, MRI and PET has an important role in the safe and effective ablation therapy. Multi planar reconstruction (MPR) imaging of these modalities which is consistent with real time ultrasound imaging can cover weak points of ultrasound imaging.

Needle navigation technology is also indispensable to monitor the needle tip during puncturing and ablation procedures even when the needle tip could not be visualized well on real time ultrasound imaging.

RFA and MWA for liver cancers and IRE (irreversible electroporation, NanoKnifeTM) for pancreatic cancer can be performed safely and effectively using contrast-enhanced ultrasound and fusion imaging technologies.

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 3: Saturday, June 22, 2019 (10:20-12:20)
ROOM A [2F] 201-202

USG Session 2

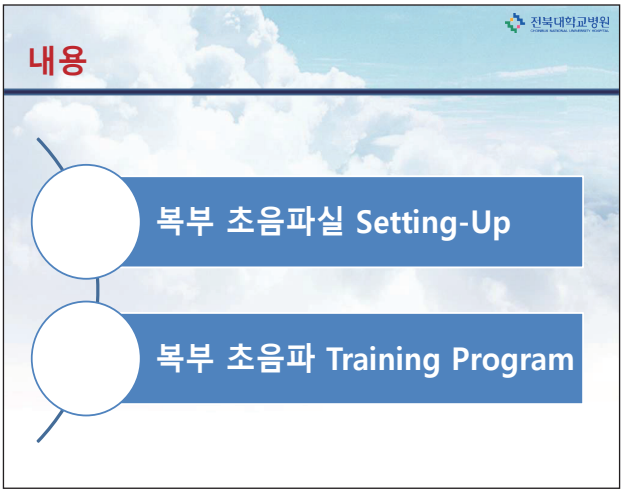
Diversifying the Field of USG for Training (*K)

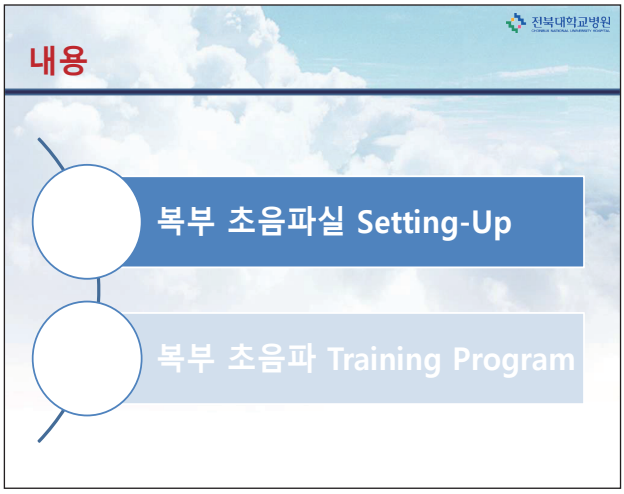
Chair:
Won Young Tak (Kyungpook National Univ.)

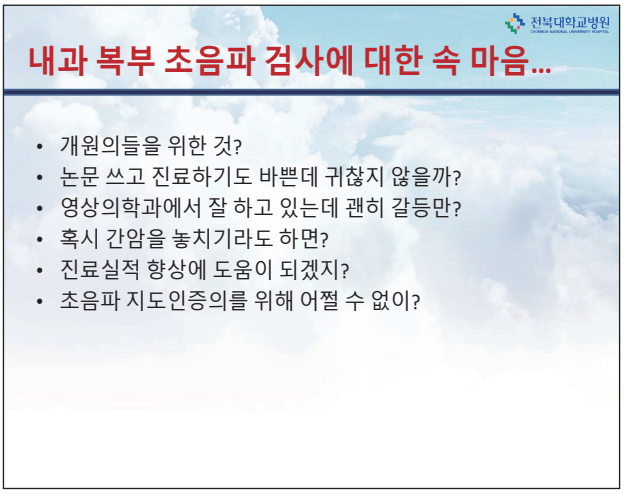
Setting-Up an Abdominal USG Facility and Training Program

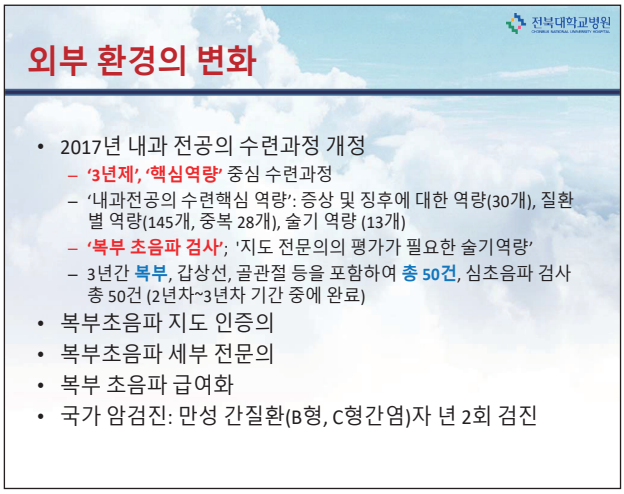
In Hee Kim

Department of Internal Medicine, Chonbuk National University Medical School and Hospital, Jeonju, Korea









복부 초음파 지도인증의

- 대한소화기학회, 대한간학회, 대한췌담도학회에서 공동으로 인정

- **"복부초음파 지도인증의"**: 복부초음파의 진단과 판독은 물론 복부초음파에 대한 교육을 담당할 수 있는 능력을 갖춘 소화기 관련 의사
- **자격 취득 기준**
  1. 대한소화기학회 또는 대한간학회 또는 대한췌담도학회 회원으로 아래의 2~4항을 모두 만족하여야 한다.
  2. **최근 5년간** 대한내과학회, 대한소화기학회, 대한간학회, 대한췌담도학회, 또는 임상초음파학회에서 인정하는 **복부초음파 지도 관련 교육에서 9 평점 이상의 교육평점**을 취득해야 한다.
  3. **최근 5년 이내**에 **200건 이상의 복부초음파 검사**를 시행하고 판독하며, 이를 입증할 수 있는 문서와 영상물 또는 복부초음파 지도인증의 인증위원회에서 요청하는 자료를 제출해야 한다. 특히, **최소 3년 이상의 시술 경력**이 입증되어야 한다.
  4. **최근 5년간** 대한내과학회, 대한소화기학회, 대한간학회, 대한췌담도학회 또는 임상초음파학회에서 주관/주최하는 학술대회에 **연자/좌장 경험이 최소 1회 이상** 있어야 한다. 단, 초음파 분야 관련 **주저자 논문 1편**의 학술활동이 있거나 **저서**를 출판한 경우 이 요건을 면제한다.

복부 초음파 세부 전문의

- **"복부 초음파 세부전문의"**: 초음파 진단과 판독에 적정 수준 이상의 능력을 갖춘 임상의사
- **자격취득기준**
  - **최근 5년 이내**에 **200건 이상의 복부 초음파**를 시행하고 판독하며, 이를 입증할 수 있는 문서와 영상물 또는 세부전문의 심사위원회에서 정하는 자료를 제출해야 한다.
  - **최근 5년 이내**에 대한간학회 세부전문의 심사위원회에서 인정하는 초음파 검사 관련 **9평점의 교육평점**을 취득해야 한다. (단, 본 학회에서 부여하는 교육평점이 4평점 이상 포함되어야 한다.)

대한간학회

초음파실 Setting-Up을 위한 기본 준비사항

1. 초음파실 공간 확보
2. 초음파 검사 장비
3. 초음파 검사 관련 물품
4. 초음파실 인력 및 역할 분담

1. 초음파실 공간 확보

- 적절한 크기의 공간
  - 접수
  - 환자 대기실, 탈의 및 개인 물품보관실
  - 초음파 검사실
  - 기타 물품보관실
  - 휴게실 등
- 적절한 위치
  - 외래 진료실, 입원 병동, 소화기 검사실(내시경실, 간섬유화 검사실), 영상의학과(CT, MRI), 진단검사의학과 등과의 연계성 고려

2. 초음파 검사 장비

- 초음파 검사 장비(본체, 탐촉자)
- 각 회사에서 소개하는 초음파 장비의 특성, 기능, 가격, A/S 등의 조건을 비교
- 실제 초음파 장비를 사용해본 검사자들의 의견 수렴
- 관심있는 초음파 장비에 대해 시연 요청
- 최종 초음파 장비 선택 후 병원 측에 구입 요청

3. 초음파 검사 관련 물품 및 환경

- 접수 및 검사실 컴퓨터, 책상, 의자 등
- 초음파실의 침대 및 시트
- 피검사자용 가운, 수건
- 초음파 검사용 젤리, 젤리 보관용 온장고
- 검사 시 적절한 간접 조명 및 조명 조절 장치

4. 초음파실 인력 및 역할분담

- 간호사(간호조무사): 환자 접수, 안내, 검사 준비
- 방사선사: 초음파 검사 장비 및 기타 물품 관리
- 검사 보조자 (전공의, 전임의): 환자 정보(검사 목적, 이전 검사 결과 등) 파악, 예비 초음파 검사 시행
- 검사자(지도전문의, 교수): 초음파 검사 시행, 판독, 교육

초음파실을 Setting-Up 할 때의 고민...

소화기내과 독립적인 초음파실 공간 확보

- 장점: 소화기 검사실(내시경, 섬유화 검사)이나 진료실과의 연계성, 새로운 장비, 독립적인 운영
- 단점: 영상의학과 견제, 병원의 소극적인 지원(예산, 인력 등)

기존 영상의학과 초음파실을 공동 이용

- 장점: 최소한의 투자, 초기 setting-up이 용이, 주변 동료(영상의학과 의사, 방사선사)의 긴밀한 협조
- 단점: 협소한 공간, 오래된 장비, 다른 소화기 검사실과 연계성 부족

초음파실 Setting-Up

- 검사 시간
  - 시행 초기(6개월 간) : 주 2 sessions (오전: 월, 수)
  - 현재 : 주 6 sessions (오전: 월, 수, 금 / 오후: 화, 목, 금)

초음파실에서 시행될 수 있는 각종 검사와 시술들

- 복부초음파 진단 검사 – B mode와 도플러 초음파 검사
- 간조직 검사
- 복수 천자 및 흉수 천자의 위치 표기나 시술
- 간농양의 흡인과 카테터 삽입
- 조영초음파 검사
- 알코올 주입술
- 고주파 열치료술

내용

복부 초음파실 Setting-Up

복부 초음파 Training Program

복부 초음파 Training Program

교수 교육
- 복부 초음파 지도 전문의

전공의 교육
전임의 교육
- 내과 전문의
- 복부 초음파 세부 전문의

교수 교육 – 기관 경험

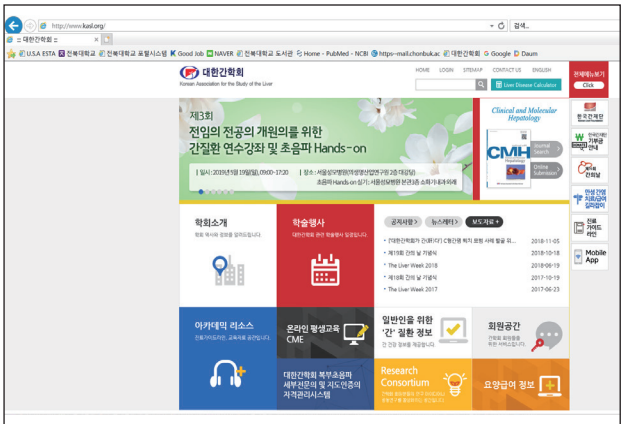
- 기관 내 영상의학과 복부전담 교수의 지도
  - 대상: 소화기내과 교수 (2인)
  - 초청강의, 초음파 참관 및 Hands-on (주 2회, 2 session)
  - 실제 검사 시행
  - 6개월 정도 소요
- 복부초음파 관련 교재, On-line 교육자료 활용
- 학회 초음파 교육(강의, Hands-on) 참석
  - 복부 초음파 지도관련 교육 9평점 이상
- 복부 초음파 시행
  - 주 1 SESSION 이상, 200건 이상

전임의 및 전공의 교육: 기관 경험

- 복부초음파 study 모임
  - 대상 : 소화기내과 전임의 및 내과 전공의
  - 시간 : 주 1회 (매주 월요일 점심시간, 30분)
  - 복부 초음파 관련 교재(복부 초음파 아틀라스, 한국의학) 리뷰
  - 2개월(3-4월)
- 복부초음파 관련 On-line 교육자료
- 교수(지도전문의) 지도하 초음파 검사 참관 및 검사 시행
  - 전공의: 25건/년 이상, 전임의: 100건/년 이상
- 학회 초음파 교육(강의 Hands-on) 이수 권고
  - 전공의: 초음파 교육 1회/년 이상
  - 전임의: 복부초음파 세부전문의 교육 3평점/년 이상

복부 초음파 STUDY 모임

- 기간 : 18주



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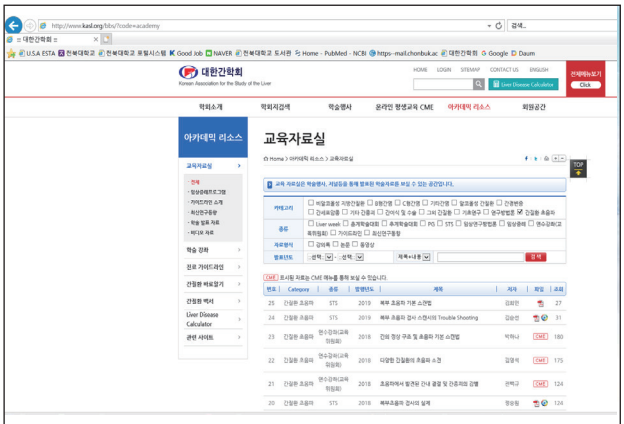
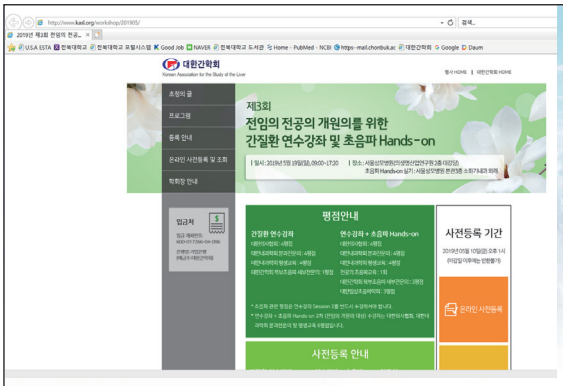


http://www.kasl.org/bbs/?code=academy

복부 초음파 교육에 유용한 On-line 교육자료

- 대한간학회 홈페이지 – 교육자료실, CME
- http://www.kasl.org/bbs/?code=academy

1. 복부 초음파 기본 스캔법
2. 복부 초음파 검사의 실제
3. 복부 초음파 검사 스캔시의 trouble shooting
4. 간의 정상구조 및 기본 스캔법
5. Standard report system for US results
6. 다양한 간질환의 초음파 소견
7. 초음파 검사에서 발견된 간내 결절 및 간종괴의 감별



- 전공의 초음파 교육: 1회
- 복부초음파 세부전문의: 3평점

초음파 검사 시행 및 전공의 교육

- 교수 감독하 전공의(전임의)가 먼저 예비 초음파 검사 시행
- 교수(지도전문의)가 검사 시행 및 판독

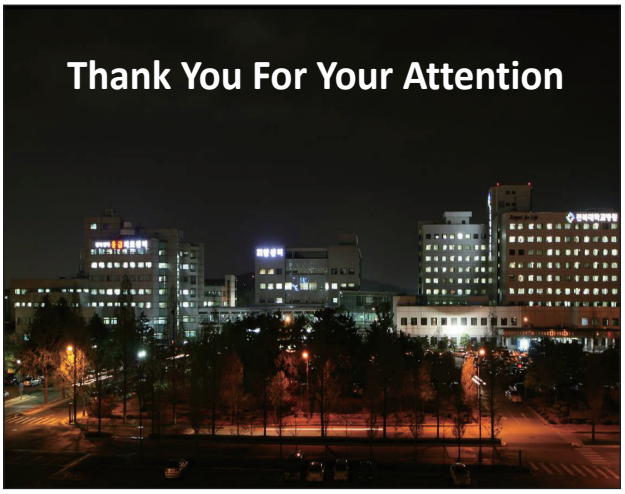
초음파 검사 시행 및 전공의 교육

	월	화	수	목	금
오전	교수1		교수2		교수3
	전임의1 전공의2		전임의1 전공의3		전임의1
오후		교수4		교수5	전임의2
		전공의2		전공의3	

- 초음파 검사 건수: 15~20건/session

결론

- 외부 환경 변화에 대한 능동적 대처 필요
- 원내 현실의 강점, 약점 등을 파악하여 초음파실 Setting-UP
  - 공간, 장비, 기타 물품, 인력 등
- 초음파 Training Program
  - 지도를 담당할 교수 교육: 지도 전문의
  - 전공의, 전임의 교육: 내과 전문의, 복부 초음파 세부전문의
  - Off-line 교육(자체 초음파 study 모임, 학회 초음파 교육, Hands-on)
  - On-line 교육(학회 홈페이지 교육자료실, CME)



Tips for Selection and Maintenance of USG Machines

Hyun Joo Kim[1], Han Jong Yu[2]

[1]GE Healthcare Korea, [2]Canon, Korea

Assessment of Hepatic Fibrosis with 2-dimensional Real-Time Shear Wave Elastography (SWE)

Joo Hyun Sohn

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Contents

- Introduction
- Measuring Liver Stiffness (LS) by 2D-SWE
- Roles of 2D-SWE in Chronic Liver Disorders
  - Assessing Liver Fibrosis
    - Various CLD
    - Viral hepatitis(CHB, HCV)
    - Non-viral CLD
  - Assessing Portal Hypertension
  - Assessing Esophageal Varices
  - Assessing the HCC Risk and Prognosis in CLD
  - Spleen Stiffness (SS) by 2D-SWE
- Summary

Elastography (Elasticity Imaging)

1. Ultrasound-based elastography:

1) One-dimensional (1-D) **transient elastography (TE)** (Sandrin et al. 2003)
2) Two-dimensional (2-D) static ultrasound elastography (Friedrich-Rust et al. 2007),
3) Acoustic radiation force impulse (**ARFI**) imaging (Fahey et al. 2008; Palmeri et al. 2008)
4) **Supersonic shear imaging** (SSI) (Muller et al. 2009), 2-D Real-time Shear Wave Elastography (SWE)
5) Shearwave dispersion ultrasound vibrometry (SDUV) (Chen et al. 2009)
6) Spatially modulated ultrasound radiation force (SMURF) imaging (McAleavey et al. 2009)
7) Sonoelastography (Taylor et al. 2000)

2. MR (magnetic resonance) elastography (Klatt et al. 2006; Muthupillai et al. 1995)

Non-invasive methods for liver fibrosis: advantages and disadvantages

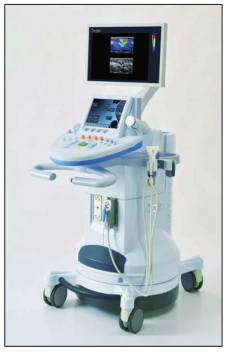
Serum biomarkers	Measurement of liver stiffness			
	Transient elastography	ARFI	SWE	MR elastography
Advantages				
• Good reproducibility • High applicability (95%) • No cost and wide availability (nonpatented) • Well validated • Can be performed in the outpatient clinic	• Most widely used and validated technique; standard to be beaten • User-friendly (performed at bedside; rapid, easy to learn) • High range of values (2–75 kPa) • Quality criteria well defined • Good reproducibility • High performance for cirrhosis (AUROC > 0.9) • Prognostic value in cirrhosis	• Can be implemented on a regular US machine • ROI smaller than TE but chosen by the operator • Higher applicability than TE (ascites and obesity) • Performance equivalent to that of TE	• Can be implemented on a regular US machine • ROI can be adjusted in size and location and chosen by the operator • Measures liver stiffness in real-time • High range of values (2–150 kPa) • Good applicability • High performance for cirrhosis	• Can be implemented on a regular MRI machine • Examination of the whole liver • High applicability: overcomes the limitations of TE (ascites and obesity) • High performance for cirrhosis
Disadvantages				
• Nonspecific of the liver • Unable to discriminate between intermediate stages of fibrosis • Performance not as good as TE for cirrhosis • Cost and limited availability (proprietary) • Limitations (hemolysis, Gilbert's syndrome, inflammation...)	• Requires a dedicated device • ROI cannot be chosen • Unable to discriminate between intermediate stages of fibrosis • Applicability (80%) lower than serum biomarker: (obesity, ascites, operator experience) • False-positive in case of acute hepatitis, extrahepatic cholestasis and congestion	• Unable to discriminate between intermediate stages of fibrosis • Units (m/s) different from that of TE (kPa) • Narrow range of values (0.5–4.4 m/s) • Quality criteria not well defined • Prognostic value in cirrhosis?	• Further validation warranted • Unable to discriminate between intermediate stages of fibrosis • Quality criteria not well defined • Learning curve? • Influence of inflammation?	• Further validation warranted especially in comparison with TE • Not applicable in case of iron overload • Requires a MRI facility • Time-consuming • Costly

Semin Liver Dis 2015;35:166–183.

US Elastography : TE vs. 2-D SWE

1st generation, Prototype

2nd generation, SWE

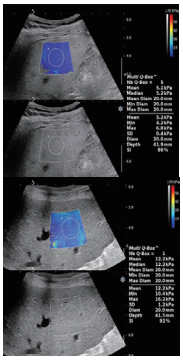


Merits of 2-D SWE vs. TE

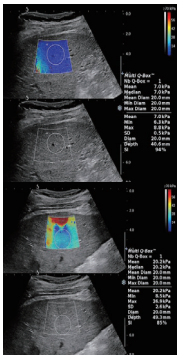
- The integration into a conventional US machine with conventional US probes during a routine standard US scan (Aixplorer version 3, Supersonic imagine, France).
- The real-time liver echo images and measurement of the liver stiffness (expressed in kilopascals, kPa) simultaneously.
- The exact localization of the ROI during B-mode US, avoiding large vessels, cysts, other structures.
- A color-coded 2-D quantitative mapping of shear elasticity, displayed in color over a conventional gray-scale B-mode image (blue to red according to low to high kPa).
- It has a larger region of interest (ROI, Q-BoxTM, 300-700mm2 area) and higher range (1~150 kPa) of measured values than TE.
- No limitation of stiffness measurement in patients with ascites.
- → LS measurements by SWE: Higher applicable, reliable, reproducible, success rates than TE

Examples: 2-D SWE Images and LS

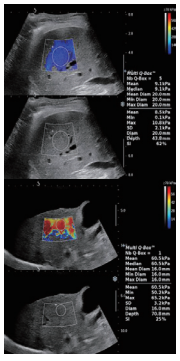
M/52, Normal, LS 5.1 kPa



M/57, CHB, F1, LS 7.0 kPa



F/58, CHB, F2, LS 9.1 kPa



M/57, CHC, F3, LS 12.2 kPa

M/54, Alc, F4, LS 20.2 kPa

F/75, LC ascites, LS 60.5 kPa

2D Real-time SWE in various chronic liver diseases: Role in predicting liver fibrosis

70 eligible subjects (adequate biopsy, valid LSM, serum markers) among 83 patients between Sep 2010 and Feb 2013; LSM by 2D-SWE, compared with serum markers

Table 1 Baseline characteristics of patients

Characteristics	n = 70	
Age, yr (SD, range)	45.9	(15.7, 12.0-82.0)
Sex, male (%)	45	(64.3)
HBV/HCV/Alcohol/NAFLD/Other (%)	23 (32.9)/18 (25.7)/12 (17.1)/4 (5.7)/13 (18.6)	
Body mass index, kg/m^2 (SD, range)	23.8	(2.9, 16.9-29.7)
Hemoglobin, g/dL (SD, range)	12.9	(2.2, 6.7-17.8)
Platelet count, 10^3/mm^3 (SD, range)	174.7	(55.3, 76.0-285.0)
Albumin, g/dL (SD, range)	3.9	(0.7, 1.6-5.3)
AST, U/L (IQR, range)	55	(31-111, 13-369)
ALT, U/L (IQR, range)	47	(24-99, 9-473)
Total bilirubin, mg/dL (IQR, range)	0.7	(0.5-1.1, 0.2-4.9)
GGT, U/L (IQR, range)	57	(31-157, 13-1569)
Prothrombin time, INR (IQR, range)	0.93	(0.87-1.00, 0.76-1.48)
APRI (IQR, range)	0.91	(0.51-1.55, 0.35-5.88)
Hyaluronic acid*, ng/mL (IQR, range)	62	(28-176, 10-2796)
Type IV collagen†, ng/mL (IQR, range)	182	(117-310, 66-2790)
Liver stiffness by SWE, kPa (IQR, range)	11.1	(7.3-18.4, 4.73-48.61)
Fibrosis stage (%)		
F0-1	15	(21.4)
F2	20	(28.6)
F3	13	(18.6)
F4	22	(31.4)

*n = 61. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamyltranspeptidase; INR: International normalized ratio; SWE: Shear wave elastography; kPa: Kilopascals; SD: Standard deviation; IQR: Interquartile range.

Jeong JY, TY Kim, Sohn JH, et al. World J Gastroenterol 2014(38): 13920-13929

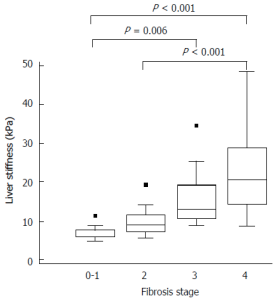
2D Real-time SWE in chronic liver diseases (CLD): Correlation with liver fibrosis and Cut-off values

LSM was well correlated with progression of fibrosis stage (r = 0.774, p < 0.001).
F0-F1: 6.77 ± 1.72,
F2: 9.98 ± 3.99,
F3: 15.80 ± 7.73, and
F4: 22.09 ± 10.09, p < 0.001).

Table 2 Liver stiffness cut-off values for the diagnosis of significant (≥ F2) and advanced (≥ F3) fibrosis and cirrhosis (F4) (n = 70)

Value	≥ F2	≥ F3	= F4
Number of patients, n (%)	55 (78.6)	35 (50.0)	22 (31.4)
Optimal cut-off* (kPa)	8.60	10.46	14.00
Sensitivity (%)	78.20	88.60	77.30
Specificity (%)	93.30	80.00	85.40
Negative likelihood ratio	11.73	4.43	5.30
Positive likelihood ratio	0.23	0.14	0.27

*Cut-off value was calculated to maximize the sum of sensitivity and specificity. kPa: Kilopascals.



Jeong JY, TY Kim, Sohn JH, et al. World J Gastroenterol 2014(38): 13920-13929

2D Real-time SWE in chronic liver diseases: Accuracy for predicting liver fibrosis

Diagnostic performance in all patients with various CLD

	AUROC	95%CI
Significant fibrosis		
SWE	0.908	0.806-0.967
HA	0.812	0.691-0.900
Type IV	0.841	0.725-0.922
APRI	0.691	0.560-0.803
Advanced fibrosis		
SWE	0.893	0.787-0.957
HA	0.897	0.792-0.960
Type IV	0.876	0.767-0.947
APRI	0.743	0.615-0.846
Cirrhosis		
SWE	0.877	0.768-0.947
HA	0.879	0.770-0.948
Type IV	0.850	0.736-0.928
APRI	0.683	0.551-0.796

Diagnostic performance in Viral CLD

	AUROC	95%CI
Significant fibrosis		
SWE	0.935	0.800-0.989
HA	0.658	0.482-0.807
Type IV	0.777	0.608-0.898
APRI	0.858	0.701-0.951
Advanced fibrosis		
SWE	0.914	0.771-0.980
HA	0.819	0.656-0.927
Type IV	0.793	0.626-0.909
APRI	0.827	0.665-0.932

Jeong JY, TY Kim, Sohn JH, et al. World J Gastroenterol 2014(38): 13920-13929

Diagnostic performance and Cut-off Values of LS by 2D SWE in various CLD

Table 1 Diagnostic performance of shear wave elastography for significant fibrosis (F ≥ 2), advanced fibrosis (F ≥ 3) and cirrhosis (F4) in patients with various liver diseases

Ref.	Year	Patients (n)	F ≥ 2 (%)	F ≥ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Jeong et al[45]	2014	70	78.6			0.915	8.60	78.2	93.3	97.7	53.8
				50		0.913	10.46	88.6	80.0	81.6	87.6
					31.4	0.878	14.00	77.3	85.4	70.8	89.2
Deffieux et al[45]	2015	120	48.0			0.890	8.90	77.0	79.0	77.0	79.0
				33		0.880	9.10	85.0	72.0	60.0	90.0
					15.0	0.890	10.20	83.0	76.0	38.0	96.0

Etiology : HBV/HCV/Alcohol/NAFLD/Other
Jeong : 23 (32.9%)/18 (25.7%)/12 (17.1%)/4 (5.7%)/13 (18.6%): F0-1(21.4%)
Deffieux : 24 (20%)/44 (36.7%)/10 (8.3%)/13(10.8%)/29(24.1%): F0-1(52%)

JY Jeong, YS Cho, JH Sohn. World J Gastroenterol 2018; 24(34): 3849-3860

Assessment of liver fibrosis by 2-D SWE:
An individual patient data-based meta-analysis (n=1134).

TABLE 1. Patient Characteristics

	All (n = 1,134)	HCV (n = 379; 33.4%)	HBV (n = 400; 35.5%)	NAFLD (n = 156; 13.8%)	Other (n = 199; 17.5%)
Gender M/n (%)	689/1,114 (61.5%)	245/379 (64.6%)	248/380 (65.3%)	72/156 (53.8%)	106/199 (54.3%)
Age (years)[†] (n = 1,116)	48.9 (13, 18-86)	48.7 (12, 19-79)	46.5 (13, 20-82)	55.7 (13, 20-80)	49.9 (14, 18-85)
Body mass index (kg/m²)[†] (n = 839)	25.9 (5.2, 16-59)	25.2 (4.1, 16-37)	24.9 (4.9, 16-59)	31.2 (5.8, 20-52)	24.5 (4.6, 18-99)
Metabolic syndromeh (%)	71/348 (20.4%)	24/158 (15.2%)	3/38 (7.9%)	39/59 (66.1%)	5/93 (5.4%)
Asahia/n (%)	1/71 (1.4%)	0/26 (0%)	0/6 (0%)	0/27 (0%)	1/12 (8.3%)
Fibrosis stage*					
0, 1 (%)	519 (45.8%)	158 (41.7%)	192 (48.0%)	65 (41.7%)	104 (52.3%)
2 (%)	251 (22.1%)	94 (24.8%)	89 (22.2%)	41 (26.3%)	27 (13.6%)
3 (%)	180 (15.9%)	58 (25.4%)	67 (16.8%)	31 (19.9%)	24 (12.1%)
4 (%)	184 (16.2%)	69 (18.2%)	52 (13.0%)	19 (12.2%)	44 (22.1%)
Activity stage*	(n = 809)	(n = 368)	(n = 102)	(n = 151)	(n = 188)
0 (%)	112 (13.8%)	16 (4.3%)	22 (21.6%)	22 (14.6%)	52 (27.7%)
1 (%)	379 (46.8%)	164 (44.6%)	57 (55.9%)	80 (53.0%)	78 (41.5%)
2 (%)	238 (29.4%)	140 (38.0%)	14 (13.7%)	40 (26.5%)	44 (23.4%)
3 (%)	80 (9.9%)	9 (13.0%)	9 (8.8%)	9 (6.0%)	14 (7.4%)
Brunt steatosis score	(n = 732)	(n = 342)	(n = 94)	(n = 121)	(n = 175)
0 (%)	310 (42.3%)	152 (44.4%)	57 (61%)	2 (1.7%)	99 (56.6%)
1 (%)	253 (34.6%)	141 (41.2%)	30 (32%)	28 (23.1%)	54 (30.9%)
2 (%)	103 (14.1%)	38 (11.1%)	5 (5%)	45 (38.8%)	17 (9.7%)
3 (%)	66 (9.0%)	11 (3.2%)	2 (2%)	46 (38.7%)	5 (2.9%)
AST (IU/L)[†] (n = 779)	72.5 (103, 8-1,583)	85.2 (119, 9-1,583)	52.0 (75, 11-756)	48.4 (29, 15-222)	83.6 (120, 8-872)
ALT (IU/L)[†] (n = 997)	91.8 (109, 9-1,473)	110.1 (118, 10-824)	76.4 (92, 9-900)	70.0 (48, 11-332)	100.7 (151, 9-1,473)
GGT (IU/L)[†] (n = 760)	156.5 (281, 8-4,344)	157.9 (334, 8-4,244)	60.8 (92, 9-690)	152.0 (245, 19-1,632)	225.9 (278, 9-1,788)
Platelet count (count 10^9/L)[†] (n = 936)	199.6 (70, 6-653)	201.5 (73, 21-437)	192.0 (94, 49-392)	213.4 (70, 60-440)	199.8 (87, 6-653)
Fastingh (%)	618/620 (99.7%)	89/91 (97.8%)	283/283 (100%)	119/119 (100%)	127/127 (100%)
Creatinine (mmol/L)[†] (n = 384)	75.7 (67, 20-901)	77.7 (92, 38-901)	80.6 (111, 45-650)	69.3 (23, 30-170)	74.9 (56, 20-559)
Albumin (g/L)[†] (n = 759)	4.25 (0.48, 1.3-5.3)	4.18 (0.50, 2.5-5.3)	4.43 (0.37, 3.1-5.3)	4.22 (0.51, 1.3-5.2)	3.94 (0.51, 2.6-5.0)
Triglyceride (mmol/L)[†] (n = 586)	1.41 (0.99, 0.3-13.1)	1.26 (0.89, 0.4-6.3)	1.35 (1.03, 0.3-13.1)	1.93 (1.12, 0.6-7.1)	1.20 (0.68, 0.4-5.2)
Fasting blood glucose (mmol/L)[†] (n = 614)	5.7 (1.9, 2.6-23.9)	5.7 (2.5, 3.1-23.9)	5.5 (1.7, 3.7-17.5)	6.3 (1.8, 2.6-12.1)	5.4 (1.7, 3.3-17.8)
Total bilirubin (μmol/L)[†] (n = 893)	18.0 (40, 4-900)	25.3 (72, 4-900)	14.4 (11, 4-139)	12.2 (12, 4-126)	19.3 (24, 4-143)

*These analyses use METAVIR stage or comparative histological assessment of liver fibrosis categorized as none or mild fibrosis (stage 0, 1), significant fibrosis (2), severe fibrosis (3), and cirrhosis (4). Correspondingly, activity stages are categorized.
†This overview does not account for the heterogeneity between sites. Continuous markers are given as mean (standard deviation, minimum-maximum).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase;

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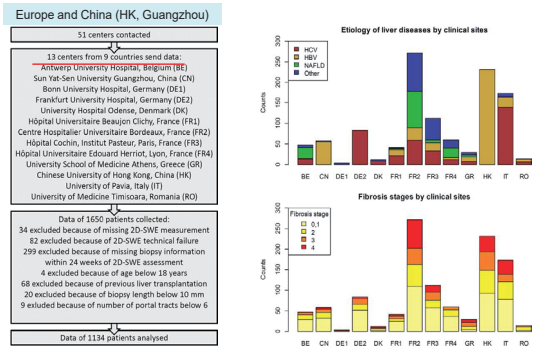
Flowchart of data collection / Heterogeneity of the etiologies of liver diseases as well as of the prevalence of the different fibrosis stages



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A meta-analysis (n=1,134):
Cut-off Values for Liver Fibrosis

TABLE 2. Evaluation of Cutoff Points for 2D-SWE

Fibrosis Stage		Estimates of Optimal Cutoff (kPa) All (n = 1,134)	HCV (n = 379)	HBV (n = 400)	NAFLD (n = 156)
0, 1 versus 2		8.25	7.095	6.95	7.15
2 versus 3		9.15	9.15	8.15	9.15
3 versus 4		9.89	13.3	10.90	11.0
		Proposed Cutoff (kPa) Other	HCV	HBV	NAFLD
≤1 versus ≥2	F2	7.1	7.1	7.1	7.1
Sensitivity (95% CI)		94.8% (85.8%-99.9%)	94.7% (85.1%-99.9%)	87.6% (81.2%-93.1%)	93.8% (84.6%-99.5%)
Specificity (95% CI)		39.9% (14.0%-68.3%)	52.0% (27.2%-76.5%)	73.6% (61.7%-84.3%)	52.0% (23.0%-80.4)
DOR (95% CI)		7.3 (2.3-22.7)	15.4 (8.0-29.5)	13.9 (8.3-23.1)	12.1 (5.1-28.6)
≤2 versus ≥3	F3	9.2	9.2	8.1	9.2
Sensitivity (95% CI)		95.1% (84.7%-100%)	90.3% (72.0%-100%)	94.9% (87.0%-99.6%)	93.1% (84.6%-99.5%)
Specificity (95%CI)		86.6% (75.8%-95.1%)	76.8% (58.5%-91.6%)	73.1% (62.6%-82.7%)	80.9% (71.1%-89.4%)
DOR (95% CI)		14.8 (6.5-33.9)	17.9 (5.5-58.8)	18.6 (10.3-33.7)	8.9 (2.8-28.6)
≤3 versus 4	F4	13.0	13.0	11.5	13.0
Sensitivity (95% CI)		79.4% (61.0%-94.0%)	85.8% (74.0%-95.1%)	79.9% (41.4%-100%)	75.3% (45.2%-97.5%)
Specificity (95%CI)		83.6% (62.5%-98.2%)	87.8% (72.5%-98.1%)	93.3% (87.6%-97.6%)	87.8% (78.0%-95.5%)
DOR (95% CI)		7.5 (1.8-31.8)	37.5 (11.7-120.4)	22.5 (3.9-128.9)	9.6 (3.2-28.4)

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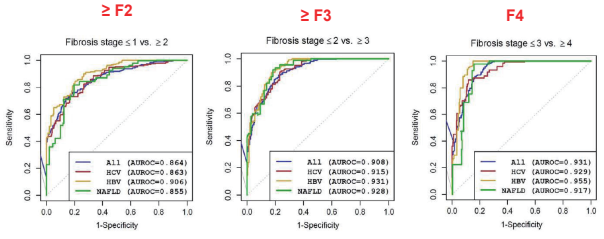
Accuracy of 2D-SWE:
Summarized ROC curves and diagnostic performance by AUROC



AUROC, 86.4%, 91%, and 93% for the diagnosis of F2, F3, F4 fibrosis of all patients: highest (90.6%, 93%, 96%) in CHB group.

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Diagnostic performance and Cut-off Values of LS by 2D SWE in CHB

Table 3 Diagnostic performance of shear wave elastography for significant fibrosis (F ≥ 2), advanced fibrosis (F ≥ 3) and cirrhosis (F4) in patients with chronic hepatitis B

Ref.	Year	Patients (n)	F ≥ 2 (%)	F ≥ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Lesing et al[74]	2013	226	60.2			0.880	7.100	84.70	92.10	85.3	91.7
				35.4		0.930	7.900	89.80	90.30	71.8	97.0
					15.5	0.980	10.100	97.40	93.00	60.1	99.6
Zeng et al[260]	2014	206 (104)	45.7 (45.1)			0.917 (0.907)	7.200	86.36 (85.19)	86.96 (80.85)	88.8 (83.6)	84.2 (82.6)
				69.0 (70.1)		0.945 (0.934)	9.100	91.94 (89.66)	85.71 (82.56)	74.0 (65.0)	96.0 (95.1)
					81.1 (83.7)	0.945 (0.967)	11.700	91.89 (88.24)	89.70 (88.10)	66.7 (60.0)	98.0 (97.4)
Wu et al[261]	2016	437	47.2			0.903	8.200	78.16	85.28	82.6	81.4
				14.0		0.926	11.256	91.80	84.31	48.7	98.4
Zhuang et al[262]	2017	304(155)	86.8 (84.6)			0.970 (0.970)	7.600	92.00 (91.6)	90.00 (87.5)	98.4 (96.0)	64.3 (65.0)
				70.4 (67.8)		0.960 (0.970)	9.200	91.60 (88.6)	96.70 (96.0)	98.5 (97.8)	82.9 (80.1)
					54.9 (48.4)	0.980 (0.980)	10.400	94.60 (92.0)	94.90 (95.0)	95.7 (94.5)	93.5 (92.7)
Zeng et al[263]	2017	257	46.3			0.882	7.100	88.89	76.38	76.2	89.0
				24.9		0.917	8.300	89.66	76.84	55.9	95.8
					13.2	0.926	11.500	93.55	87.25	52.7	98.9
Herrmann et al[60]	2018	379	52.0			0.906	7.100	87.60	73.60		
				29.8		0.931	8.100	94.90	73.10		
					13.0	0.955	11.500	79.90	93.90		

[†]These studies are divided into index cohort and validation cohort and parentheses are index cohort. AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

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Diagnostic performance and Cut-off Values of LS by 2D SWE in CHC

Table 2 Diagnostic performance of shear wave elastography for significant fibrosis (F ≥ 2), advanced fibrosis (F ≥ 3) and cirrhosis (F4) in patients with chronic hepatitis C

Ref.	Year	Patients (n)	F ≥ 2 (%)	F ≥ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Bavu et al[263]	2011	113	55.8			0.950	9.12	81.0	72.0		
				34.5		0.960	10.08	75.0	78.0		
					13.3	0.970	13.30	80.0	87.0		
Ferraioli et al[47]	2012	121	58.7			0.920	7.10	90.0	87.5	91.3	85.7
				31.4		0.960	8.70	97.3	95.1	90.0	98.7
					19.8	0.980	10.40	87.5	96.8	87.5	96.8
Tada et al[48]	2013	55	32.7			0.940	8.80	88.9	91.9	84.2	94.4
Herrmann et al[60]	2018	379	58.3			0.863	7.10	94.7	52.0		
				33.5		0.915	9.20	90.3	76.8		
					18.2	0.929	13.00	85.8	87.8		

JY Jeong, YS Cho, JH Sohn. World J Gastroenterol 2018; 24(34): 3849-3860

Diagnostic performance and Cut-off Values of LS by 2D SWE in **non-viral liver diseases**

Table 4 Diagnostic performance of shear wave elastography for significant fibrosis (F ⩾ 2), advanced fibrosis (F ⩾ 3) and cirrhosis (F4) in patients with non-viral liver diseases

Ref.	Year	Etiology	Patients (*n*)	F ⩾ 2 (%)	F ⩾ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Cassinotto *et al*[28]	2016	NAFLD	291	70.8			0.860	8.90	68.0	94.0		
					43.3		0.890	9.30	84.0	83.0		
						16.8	0.880	10.00	95.0	69.0		
Takeuchi *et al*[29]	2018	NAFLD	71	64.8			0.750	11.57	52.0	44.0		
					45.1		0.820	13.07	63.0	57.0		
						7.0	0.900	15.73	100.0	82.0		
Herrmann *et al*[30]	2018	NAFLD	156	58.3			0.855	7.10	93.8	52.0		
					32.1		0.928	9.20	93.1	80.9		
						12.2	0.917	13.00	75.3	87.8		
Thiele *et al*[19]	2016	Alcohol	199	42.0			0.940	10.20	82.0	93.0	90.0	88.0
						18.0	0.950	16.40	94.0	91.0	71.0	99.0
Zeng *et al*[20]	2017	Autoimmune	114	71.9			0.850	9.70	81.7	81.3	91.8	63.4
					41.3		0.850	13.20	83.0	74.6	69.6	86.2
						20.2	0.860	16.30	87.0	80.2	52.6	96.1
Li *et al*[30]	2018	Autoimmune	51	35.2			0.781	9.15	83.3	72.7		

In NAFLD patients, there is a relatively high failure rate (2.7%-13%) because of the higher BMIs. Diagnostic performance in predicting each fibrosis stage was relatively low, and the cut-off values of the fibrosis stages varied between the studies.

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Comparison between 2D SWE vs. TE

Paired TE and 2D-SWE evaluations were performed in 665 (58.6%) among 1134 total patients

Table S3: Patient characteristics for the 665 patients with paired TE and 2D-SWE evaluations with reported success and IQR/median ≤ 0.3 for the TE assessments.

	All	HCV	HBV	NAFLD
N (%)	665	271 (40.8)	206 (31.0)	91 (13.7)
Gender M/N (%M)	414/665 (62.3)	174/271 (64.2)	139/206 (67.5)	52/91 (50.5)
Age [year][2] (n=665)	49.2 (13, 19-83)	48.0 (13, 18-79)	47.2 (13, 21-82)	51.1 (12, 20-83)
BMI [kg/m²][2] (n=577)	25.3 (4.6, 16-45)	24.9 (3.9, 16-37)	23.9 (3.8, 16-35)	30.7 (5.4, 20-45)
Metabolic Syndrome /N (%)	40/165 (24.2%)	17/96 (17.7%)	1/13 (7.7%)	19/28 (67.9%)
Ascites/N (%)	0/11 (0%)	0/6 (0%)	0/4 (0%)	0/1 (0%)
Fibrosis Stage[1]				
0,1 (%)	284 (42.7%)	115 (42.4%)	90 (43.7%)	33 (36.3%)
2 (%)	156 (23.5%)	66 (24.4%)	52 (25.2%)	22 (24.2%)
3 (%)	103 (15.5%)	40 (14.8%)	35 (17.0%)	21 (23.1%)
4 (%)	122 (18.3%)	50 (18.5%)	29 (14.1%)	15 (16.5%)

2D SWE > TE for all fibrosis stages

- In HCV, HBV, or NAFLD patients, AUROCs were 4.2%-11.2% larger using 2D-SWE for the diagnosis of F2 fibrosis (absolute differences, p< 0.001 in HBV patients, p=0.001 in all patients).
- AUROCs were 1.4%-12.8% larger using 2DSWE for the diagnosis of F3 fibrosis (p = 0.003 in NAFLD patients, p= 0.035 for all patients)
- For the diagnosis of F4 cirrhosis, AUROCs were about 1.4%-6.7% larger using 2D-SWE versus TE (p = 0.007 in HBV patients, p =0.022 for all patients)
- The gain in AUROC with 2D-SWE when compared with TE was largest in HBV patients and smallest in HCV patients.

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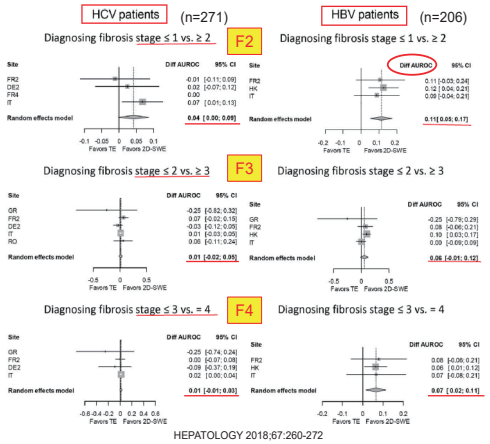
SWE > TE in AUROC for the diagnosis of F2, F3, F4 Fibrosis



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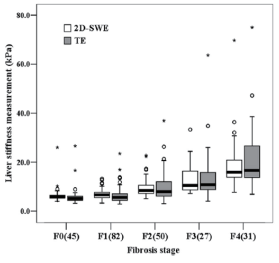
Comparison between 2D SWE and TE for liver fibrosis staging in Chinese patients with CHB (n=257): TE = 2D SWE

Table 1. Demographic characteristics and biochemical and histologic data of patients with chronic hepatitis B infection (n = 257)

Age, y	36.7, 9.4, 18–65*
No. of men	199 (77.4%)
Body mass index, kg/m²	21.7 (19.7–23.9) [14.4–32.9]†
Aspartate aminotransferase, IU/L	32.0 (24.3–50.8) [13.0–484.0]†
Alanine aminotransferase, IU/L	42.0 (28.3–67.8) [7.0–736.0]†
Alkaline phosphatase, IU/L	69.0 (55.0–83.8) [33.0–245.0]†
γ-Glutamyl transferase, IU/L	29.0 (20.0–54.0) [7.0–1615.0]†
Total bilirubin, μmol/L	13.0 (10.7–17.7) [3.8–247.7]†
Serum albumin, g/L	44.2 (41.3–46.7) [18.3–51.6]†
Platelets count, 10^9/L	186.0 (151.3–228.0) [47.0–472.0]†
Prothrombin time, %	99.0, 12.5, 56.0–136.0*
METAVIR fibrosis stage	
F0	48 (18.6%)
F1	90 (35.0%)
F2	55 (21.4%)
F3	30 (11.7%)
F4	34 (13.2%)

* Mean, SD, range.
† Median (interquartile range) [range].



Ultrasound in Medicine & Biology, 2017:43, 1563-1570

Characteristics	Method	METAVIR stage F0	F1	F2	F3	F4
Median, kPa	2-D SWE	6.0	6.6	8.5	10.5	15.9
	TE	5.2	5.6	7.9	10.8	16.6
Interquartile range	2-D SWE	5.3–6.6	5.5–7.8	7.2–10.7	8.6–16.6	13.7–20.8
	TE	4.4–6.2	4.4–7.2	6.1–12.3	8.7–16.0	13.3–27.0
Range	2-D SWE	4.0–26.0	5.2–33.2	5.0–22.7	7.2–33.3	7.7–69.7
	TE	3.2–26.6	2.9–23.5	3.1–36.9	4.1–63.6	6.9–75.0
p Value*	2-D SWE		0.013	<0.001	0.018	0.005
	TE		0.207	<0.001	0.037	0.004

SWE = shear wave elastography; TE = transient elastography.
* *p* values refer to differences between consecutive fibrosis stages.

Table 3. Performance characteristics of 2-D SWE and TE for staging liver fibrosis in patients with chronic hepatitis B infection*

Parameter	Method	≥F2 (95% CI)	≥F3 (95% CI)	F = 4 (95% CI)
Area under curve	2-D SWE	0.882 (0.834–0.920)	0.917 (0.874–0.949)	0.926 (0.885–0.956)
	TE	0.849 (0.797–0.893)	0.883 (0.835–0.921)	0.909 (0.865–0.943)
Cutoff, kPa	2-D SWE	7.1	8.3	11.3
	TE	7.3	8.6	11.2
Sensitivity, %	2-D SWE	88.89 (81.4–94.1)	89.66 (78.8–96.1)	93.55 (78.6–99.2)
	TE	78.70 (69.8–86.0)	86.21 (74.6–93.9)	93.55 (78.6–99.2)
Specificity, %	2-D SWE	76.38 (68.0–83.5)	76.84 (69.9–82.8)	87.25 (81.9–91.5)
	TE	81.10 (73.2–87.5)	77.97 (71.1–83.8)	82.84 (77.0–87.7)
PPV, %	2-D SWE	76.2 (67.8–83.3)	55.9 (45.2–66.3)	52.7 (38.7–66.5)
	TE	78.0 (69.0–85.4)	56.2 (45.2–66.7)	45.3 (32.7–58.4)
NPV, %	2-D SWE	89.0 (81.6–94.2)	95.8 (91.0–98.4)	98.9 (96.0–99.9)
	TE	81.7 (73.8–88.1)	94.5 (89.5–97.6)	98.8 (95.8–99.9)
LR+	2-D SWE	3.76 (2.7–5.2)	3.87 (2.9–5.1)	7.34 (5.1–10.6)
	TE	4.16 (2.9–6.1)	3.91 (2.9–5.3)	5.45 (4.0–7.5)
LR−	2-D SWE	0.15 (0.08–0.3)	0.13 (0.06–0.3)	0.074 (0.02–0.3)
	TE	0.26 (0.2–0.4)	0.18 (0.09–0.3)	0.078 (0.02–0.3)

LR+ (LR−) = positive (negative) likelihood value; PPV (NPV) = positive (negative) predictive value; SWE = shear wave elastography; TE = transient elastography.
* Characteristics are based on optimal cutoff elasticity values. Pathologic analysis was the diagnostic reference standard.

Comparison with TE vs. SWE vs. MRE: a Meta-Analysis

NAFLD (n=13,046; 28/64 studies: TE(19), SWE(4), MRE(5))

The summary AUROC values using **FibroScan M probe, XL probe, SWE, and MRE** for diagnosing **Advanced Fibrosis** were 0.88, 0.85, 0.95, and 0.96, respectively(FS vs. SWE, MRE, all p values < 0.01).

MRE and SWE may have the highest diagnostic accuracy for staging fibrosis in NAFLD patients. **(SWE=MRE>TE)**

TABLE 1. AUC Values of APRI, FIB-4, BARD Score, NAFLD Score, FibroScan, SWE, and MRE for Detecting SF, AF, and Cirrhosis

	No. of Studies (No. of Patients)	AUC Value (Mean)	95% Confidence Interval	AUC Value (Range)
APRI				
SF	11 (2352)	0.70	0.64-0.76	0.54-0.87
AF	29 (6746)	0.75	0.72-0.77	0.60-0.92
Cirrhosis	11 (2196)	0.75	0.70-0.80	0.60-0.84
FIB-4				
SF	12 (3330)	0.76	0.70-0.79	0.59-0.84
AF	34 (8246)	0.80	0.77-0.84	0.37-0.95
Cirrhosis	8 (1872)	0.85	0.81-0.89	0.78-0.91
BARD score				
SF	5 (1330)	0.64	0.53-0.75	0.50-0.73
AF	30 (7791)	0.73	0.71-0.75	0.64-0.87
Cirrhosis	5 (1260)	0.70	0.63-0.77	0.62-0.75
NAFLD score				
SF	11 (2096)	0.72	0.65-0.79	0.55-0.88
AF	38 (9245)	0.78	0.75-0.81	0.52-0.96
Cirrhosis	8 (1830)	0.83	0.76-0.89	0.68-0.92
FibroScan M probe				
SF	15 (2207)	0.83	0.79-0.86	0.67-1.00
AF	16 (2496)	0.87	0.83-0.90	0.75-0.98
Cirrhosis	12 (1830)	0.93	0.90-0.94	0.86-0.96
FibroScan XL probe				
SF	3 (318)	0.82	0.75-0.89	0.80-0.85
AF	3 (318)	0.86	0.78-0.94	0.84-0.90
Cirrhosis	3 (318)	0.94	0.88-0.99	0.91-0.95
SWE				
SF	2 (233)	0.89	0.46-1.00	0.88-0.92
AF	3 (429)	0.91	0.82-1.00	0.88-0.95
Cirrhosis	1 (181)	0.93	—	—
MRE				
SF	3 (384)	0.88	0.83-0.92	0.86-0.89
AF	5 (628)	0.93	0.90-0.97	0.89-0.96
Cirrhosis	3 (384)	0.92	0.80-1.00	0.88-0.97

HEPATOLOGY 2017;66:1486-1501

Portal Hypertension (PH)
Diagnosis Modalities

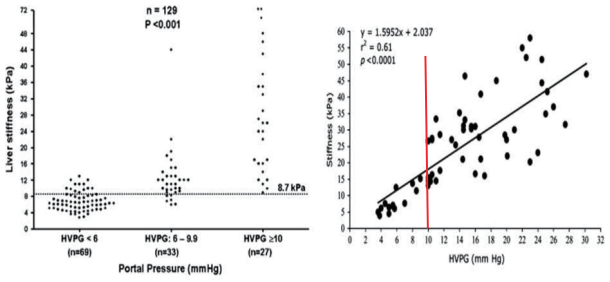
Invasive

- **HVPG** (Hepatic Venous Pressure Gradient) measurement is a relevant gold standard for assessing the degree of portal hypertension (PHT).
- HVPG = WHPG-FHVP

Non-invasive

- CT angiography
- MR angiography
- USG
- Doppler US
- EUS
- Liver Stiffness by US (TE, SWE)
- MR elastography of liver, spleen
- Portal scintigraphy using ^{99m}Tc
- Biomarkers

Role of TE in the evaluation of PH:
Relationship between liver stiffness by TE and HVPG



The correlation was excellent for HVPG values less than 10 or 12 mmHg (r = 0.81, P < 0.0003 and r = 0.91, P < 0.0001, respectively), but it was not optimal for HVPG values >10 or > 12 mmHg.
TE cannot measure the complex hemodynamic changes, characteristics of severe PH and is not useful in the monitoring the hemodynamic response to drug therapy. (Castera L. J Hepatol 2008;48:835)

TE is unsuccessful and limited to use in cirrhotic patients with perihepatic ascites.

Diagnostic performance of TE
Clinically significant portal hypertension (CSPH, HVPG ≥10 mmHg)

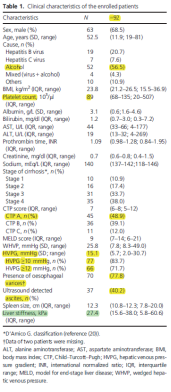
Table 2. Diagnostic performance of transient elastography for the detection of clinically significant portal hypertension (HVPG ≥10 mm Hg).

Authors, [Ref.]	Patients (n)	Etiologies	Study design	Prevalence of clinically significant portal hypertension (%)	Cut-offs HVPG ≥10 mmHg (kPa)		AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR
Carrion *et al.*, [35]	124	HCV-LT	Pro. mono.	21	8.7*	-	0.92	90	81	81	90	4.7	0.12
Vizzutti *et al.*, [36]	61	HCV	Pro. mono.	77	13.6	17.6**	0.99 0.92	97 94	92 81	97 86	92 91	13.7 4.9	0.02 0.08
Sanchez-Conde *et al.*, [39]	38	HIV-HCV	Pro. mono.	74	14.0	23.0**	0.80 0.80	93 83	50 67	84 79	71 71	3.5 2.5	0.62 0.49
Lemoine *et al.*, [38]	44 48	HCV Alcohol	Retro. mono.	77 83	20.5 34.9		0.76 0.94	63 90	70 88	88 97	35 64	2.1 7.5	0.53 0.13
Bureau *et al.*, [37]	150	CLD	Pro. mono.	51	21.0		0.94	90	93	93	91	12.8	0.10

*Hepatic venous pressure gradient (HVPG) ≥6 mm Hg; **severe portal hypertension HVPG ≥12 mm Hg.
AUC, area under ROC curve; Se, sensitivity; Sp, specificity; +LR, positive likelihood ratio; –LR, negative likelihood ratio; HCV, chronic hepatitis C; HCV-LT, liver transplant for hepatitis C; CLD, chronic liver diseases; Pro. mono., prospective monocentric; Retro. mono., retrospective monocentric.

J Hepatol. 2012 Mar;56(3):696-703.

Role of 2D-SWE in Portal Hypertension



- 92 among 115 cirrhotic patients were eligible for analysis
- LSM using real-time 2D-SWE is well correlated (r = 0.65, p<0.001) with the value of HVPG in cirrhotic patients regardless of the presence of ascites.
- SWE is a new reliable non-invasive tool to predict both clinically significant and severe portal hypertension, even in cirrhotic patients with ascites.

Kim TY, Jeong WK, Sohn JH, et al. Liver Int. 2015; 35: 2416–2424.

2D-SWE Role in predicting CSPH and SPH

Table 3. Performance of platelet count and liver stiffness (LS) values for predicting clinically significant and severe portal hypertension (CSPH and SPH) according to optimal cut-off values

Degree of PH	Parameters	AUROC	95% CI	*P* value	COV	Sn	Sp	PPV	NPV	Diagnostic accuracy	OR	95% CI
CSPH (n = 77, 83.7%)	Platelet count (10^3/μl)	0.681	0.567–0.775	0.026	142	87.0	53.3	90.5	44.4	81.5	7.66	2.28–25.75
	LS values (kPa)	0.819	0.725–0.892	<0.001	15.2	85.7	80.0	95.7	52.2	84.8	24.00	5.82–99.00
SPH (n = 66, 71.7%)	Platelet count (10^3/μl)	0.598	0.491–0.699	0.146	122	78.8	53.8	81.3	50.0	71.7	4.33	1.64–11.44
	LS values (kPa)	0.867	0.780–0.928	<0.001	21.6	83.3	80.8	91.7	65.6	82.6	21.00	6.51–67.70

AUROC, areas under the receiver operating characteristic; COV, cut-off value; NPV, negative predictive values; OR, odds ratio; PH, portal hypertension; PPV, positive predictive values; Sn, sensitivity; Sp, specificity.

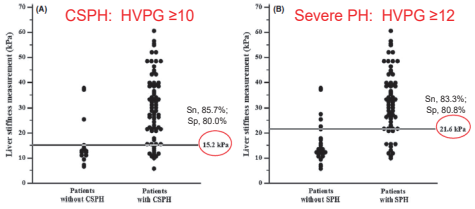


Fig. 2. The distribution of LSM between patients with CSPH and those without CSPH (A) and patients with SPH and those without SPH (B). CSPH, clinically significant portal hypertension; LSM, liver stiffness measurement; SPH, severe portal hypertension.

Kim TY, Jeong WK, Sohn JH, et al. Liver Int. 2015; 35: 2416–2424.

2D-SWE in predicting CSPH (HVPG ≥10)

Table 5 Diagnostic performance of shear wave elastography for detecting clinically significant portal hypertension (HVPG ≥ 10 mmHg)

Ref.	Year	Patients (n)	Study design	Prevalence (%)	Site	Success rate (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Procopet *et al*[34]	2015	88	Rastospective	55.0	LS	99.0	17.0	0.859	80.8	82.1		
							15.4*	0.948	91.3	90.9		
					SS	66.0		0.725				
Elkrief *et al*[35]	2015	79	Prospective	90.9	LS	97.0	24.5	0.870	81.0	88.0	98.0	35.0
					SS	97.0	34.7	0.640	40.0	100.0	100.0	18.0
Kim *et al*[36]	2015	92	Prospective	83.7	LS	98.3	15.2	0.819	85.7	80.0	95.7	52.2
							21.6†	0.867	83.3	80.8	91.7	65.6
Jansen *et al*[37]	2017	109	Prospective multicenter	67.9	LS	100.0	24.6	0.860	68.3	80.4	87.7	55.4
					SS	81.2	26.3	0.840	79.7	84.2	90.8	68.0

*Highly reliable and reliable measurements (n = 43): SD/median > 0.10 or depth ≥ 5.6 cm; †Severe portal hypertension (HVPG ≥ 12 mmHg). AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LS: Liver stiffness; SS: Spleen stiffness.

Jansen, et al. Liver Int. 2017 Mar;37(3):396-405 :
alcohol/**viral** hepatitis/NASH/others : 89/12/27/30(56.3/ **7.6**/17.1/19%)n=158

JY Jeong, YS Cho, JH Sohn. World J Gastroenterol 2018; 24(34): 3849-3860

SWE as a Quantitative Biomarker of CSPH: A Systematic Review and Meta-Analysis

Sensitivity and specificity of SWE for diagnosing CSPH

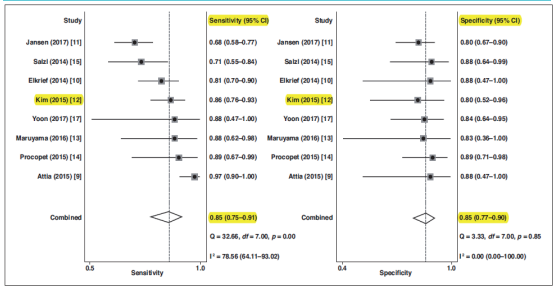


Fig. 4.—Coupled forest plots of sensitivity (*left*) and specificity (*right*) of shear wave elastography for diagnosing clinically significant portal hypertension. Dashed lines = summary value, squares = sensitivity or specificity for each study, horizontal lines = 95% CI for each study, diamonds = 95% CI for summary value.

AJR 2018; 210:W185–W195

Role of SWE in Detecting Esophageal Varices

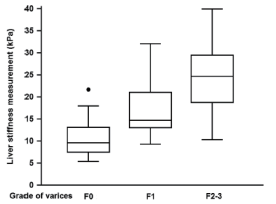
Patients With Compensated Cirrhosis (n=103)

Table 1. Baseline Characteristics of the Patients

Characteristic	Value
Age, y	53.5 ± 11.8 (20–80)
Male	67 (65.0)
Etiology of cirrhosis	
Hepatitis B virus	52 (50.5)
Hepatitis C virus	9 (8.7)
Alcohol	29 (28.2)
Hepatitis B virus + alcohol	8 (78)
Hepatitis C virus + alcohol	1 (1.0)
Other	4 (3.9)
BMI, kg/m²	24.3 ± 2.8 (18.2–31.6)
Platelets, 10³/mm³	121 (84–121; 16–360)
Albumin, g/dL (IQR, range)	4.3 (3.7–4.6; 2.8–5.3)
AST, U/L	35 (26–56; 12–241)
ALT, U/L	26 (19–45; 7–266)
Total bilirubin, mg/dL	0.8 (0.5–1.2; 0.2–2.9)
Prothrombin time, INR	0.94 (0.90–1.00; 0.79–1.24)
Spleen diameter, cm	10.5 (9.6–12.1; 7.7–17.1)
PC/SD ratio, (N/mm³)/mm	1159 (752–1716; 111–4670)
Liver stiffness, kPa	12.1 (8.9–16.1; 5.4–39.9)
Esophageal varices	
F0	63 (61.2)
F1	27 (26.2)
High-risk (F2 or F3)	13 (12.6)

Data are presented as mean ± SD (range), number (percentage), or median (IQR; range). AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; INR, international normalized ratio; and PC/SD, platelet count/spleen diameter.

Figure 4. Box-and-whisker plots of liver stiffness values according to the degrees of esophageal varices. Boxes denote IQRs (ie, 25th–75th percentiles) of liver stiffness measurements by SWE; lines inside the boxes denote medians (ie, 50th percentiles); and the dot denotes an outlier.



* F0 = no varices, 9.6 kPa (IQR, 7.4–13.3 kPa); F1 EV, 14.7 kPa (IQR, 13.0–21.5 kPa); and F2-3 high-risk EV, 24.7 kPa (IQR, 18.4–30.3 kPa)

Kim TY, , Sohn JH, et al. J Ultrasound Med 2016; 35:1373–1381

Comparison between LS by SWE and Other Common Predictors for Esophageal Varices in Patients with Compensated Cirrhosis

Table 3. Platelet, Spleen Diameter, Platelet Count/Spleen Diameter Ratio, and Liver Stiffness Values for Predicting the Presence of Esophageal Varices and High-risk Varices According to Optimal Cutoff Values

Characteristic	AUROC	95% CI	*P*	COV	Se, %	Sp, %	+LR	–LR
Esophageal varices (n = 40 [38.8%])								
Platelets, 10³/mm³	0.765	0.672–0.843	<.001	104	70.0	76.2	2.94	0.39
Spleen diameter, cm	0.692	0.594–0.780	<.001	10.7	67.5	68.3	2.13	0.48
PC/SD ratio, (N/mm³)/mm	0.770	0.677–0.848	<.001	860	62.5	82.5	3.58	0.45
Liver stiffness, kPa	0.887	0.809–0.941	<.001	13.9	75.0	88.9	6.75	0.28
High-risk varices (n = 13 [12.6%])								
Platelets, 10³/mm³	0.845	0.761–0.909	<.001	89	84.6	81.1	4.48	0.19
Spleen diameter, cm	0.722	0.625–0.806	.008	13.7	53.8	93.3	8.08	0.49
PC/SD ratio, (N/mm³)/mm	0.841	0.755–0.905	<.001	824	84.6	80.0	4.23	0.19
Liver stiffness (kPa)	0.880	0.801–0.936	<.001	16.1	84.6	85.6	5.86	0.18

COV indicates cutoff value; LR, likelihood ratio; PC/SD, platelet count/spleen diameter; Se, sensitivity; and Sp, specificity.

Table 4. Multivariate Logistic Regression Analysis for the Presence of Esophageal Varices and High-risk Varices

Characteristic	Esophageal Varices OR	95% CI	*P*	High-risk Varices OR	95% CI	*P*
Liver stiffness, kPa	1.517	1.220–1.888	<.001	1.201	1.042–1.384	.012
PC/SD ratio, (N/mm³)/mm	0.881	0.781–0.993	.038	0.851	0.697–1.040	.115

PC/SD indicates platelet count/spleen diameter.

Kim TY, , Sohn JH, et al. J Ultrasound Med 2016; 35:1373–1381

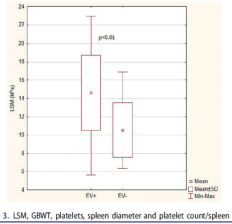
Role of SWE in evaluating Esophageal Varices in Patients With Compensated Cirrhosis

- The optimal cutoff values of LS for predicting the presence of esophageal varices and high-risk varices were 13.9 and 16.1 kPa, respectively.
- The AUROC of liver stiffness for prediction of esophageal varices was significantly higher than the AUROCs of platelet count, spleen diameter, and platelet count/spleen diameter ratio (P = .025; P = .001; P = .027).
- For predicting esophageal varices in patients without splenomegaly, the AUROC of liver stiffness was higher than that of the platelet count/spleen diameter ratio.
- In multivariate logistic regression analysis, liver stiffness and the platelet count/spleen diameter ratio were independent predictors of esophageal varices (P < .001; P = .038).
- For the presence of high-risk varices, only liver stiffness was a statistically significant independent predictor (P = .012).

→ In patients with compensated cirrhosis, liver stiffness measured by SWE is a new effective noninvasive diagnostic tool for predicting the presence of esophageal varices, and is more accurate than the platelet count/spleen diameter ratio, especially in patients without splenomegaly.

Kim TY, , Sohn JH, et al. J Ultrasound Med 2016; 35:1373–1381

Diagnostic accuracy of 2D-SWE for predicting EV



The group with EV (51/100) had a mean LSM of 14.60 (±4.11) kPa.
Vs.
The group without EV (49/100) had a mean LSM of 10.55 (±3.00) kPa.

Cut-off value = 13.6 kPa

Table 3. LSM, GBWT, platelets, spleen diameter and platelet count/spleen diameter ratio for predicting the presence of EV according to optimal cut-off values.

Characteristic	AUROC	95% CI	*p*	Cut-off	Sen %	Spe %	PPV	NPV
EV (n = 51, 51%)								
LSM (kPa)	0.781	0.692–0.871	<.001	13.58	60.8	83.7	0.795	0.672
GBWT (mm)	0.707	0.601–0.814	<.001	3.07	68.6	77.6	0.800	0.704
Spleen diameter (mm)	0.672	0.565–0.779	.004	118.5	75.0	55.1	0.635	0.679
Platelets (10^3/μl)	0.635	0.526–0.744	.021	118	52.0	73.5	0.671	0.595
PC/SD ratio ((N/μm)/mm)	0.686	0.580–0.792	.002	1112	59.6	73.5	0.701	0.636

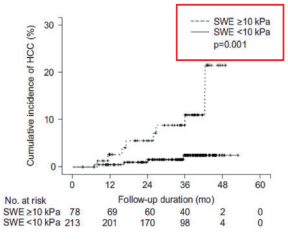
EV: esophageal varices; AUROC: area under the receiver operating characteristic curve; CI: confidence interval; p: p value; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; LSM: liver stiffness measurement; GBWT: gall bladder wall thickening; PC/SD: platelet count / spleen diameter.

Scand J Gastroenterol. 2019 Mar 17:1-8. doi: 10.1080/00365521.2019.1585571. [Epub ahead of print]

2D-SWE Role in Evaluating the Risk of HCC: Korean patients with CHB (n= 291)

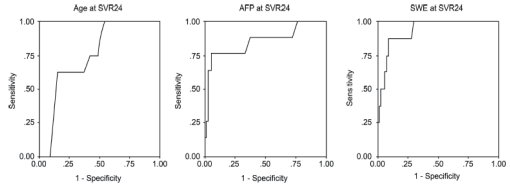
- Based on a multivariable analysis, older age (≥50 years) and higher LS value (≥10 kPa) were independently associated with the risk of developing HCC (hazard ratio [HR], 4.53, p=0.023; and HR, 4.08, p=0.022).
- The cumulative incidence rate of HCC was significantly higher in patients with higher LS values (≥10 kPa) than in those with lower LS values (<10 kPa) (p=0.001).
- The cumulative rates of HCC at 1-, 2-, and 4-years were 0.5%, 1.6%, and 2.5%, respectively, in patients with LS values <10 kPa, and 2.6%, 5.5%, and 21.5%, respectively, in patients with LS scores ≥10 kPa.
- The time-dependent AUROCs of LS measurement by SWE for HCC development at 1-, 2-, 3-, 4-, and 5-year were 0.76, 0.71, 0.77, 0.75, and 0.75, respectively.

Measured by 2D-SWE between 2011 and 2012
291 eligible subjects among 446 CHB patients
Median follow-up for 3 years
Mean age = 46.8 years
Cirrhosis in 14%
Antiviral treatment in 56.7%



Jeong JY, Sohn JH, et. al. Gut and Liver 2017, 1: 852-859

SWE predicts HCC risk in CHC patients after SVR24 (n=196)



Variables	AUC	95% CI	Cutoff	Sensitivity	Specificity	NPV	PPV
Age (years)	0.746	0.618-0.874	75	0.625	0.824	0.981	0.132
AFP (ng/mL)	0.845	0.674-1.015	6	0.750	0.926	0.989	0.300
SWE (kPa)	0.933	0.868-0.998	11	0.750	0.915	0.989	0.273

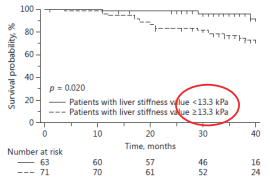
Fig 3. Predictive values for age, AFP, and SWE levels. ROC curve for predicting the development of HCC. Area under the ROC curve, 95% CI, cutoff value, sensitivity, specificity, negative predictive value (NPV), and positive predictive value are also shown.

PLoS ONE 13(4):e0195173. April, 2018
https://doi.org/10.1371/journal. pone.0195173

LSM by 2D-SWE: Prognostic Value after RFA for HCC

Characteristic	Value
Age, years	61.7±8.3 [38–84]
Gender	
Males	99 (73.9)
Females	35 (26.1)
Etiology of liver disease	
HBV-related	112 (83.6)
HCV-related	12 (9.0)
Alcoholic	6 (4.5)
Others[1]	4 (2.9)
Prothrombin activity (INR)	1.09±0.10 [0.91–1.58]
Serum albumin, g/L	37.7±3.9 [29–47]
Total bilirubin level, mg/dL	0.89±0.35 [0.20–1.90]
Serum AFP level, ng/mL	252.8±1,279.0 [1.0–10,650.0]
FIB-4 index	4.76±3.38 [0.79–22.77]
Tumor number	
1	112 (83.6)
2	17 (12.7)
3	5 (3.7)
Tumor size (largest one), cm	1.7±0.65 [1.0–3.6]
Previous treatment history for HCC	
No	53 (39.6)
Surgical resection	10 (7.5)
Ablation	12 (9.0)
Transarterial chemoembolization	33 (24.6)
More than two modalities	26 (19.3)
Antiviral therapy	
Yes	97 (72.4)
No	37 (27.6)

134 patients with 161 HCCs
Between January 2012 and December 2013
A mean follow-up of 33.8 ± 9.9 month



Liver Cancer 2018;7:65–75

LSM by 2D-SWE: Prognostic Value after RFA for HCC (n=134, 161 HCCs)

Table 2. Cox survival analysis of the predictors of overall survival in 134 patients with 161 HCCs after RFA

Characteristic	Univariate HR	95% CI	p value	Multivariate HR	95% CI	p value
Gender (male)	0.65	0.22–1.94	0.439			
Age (per 1 year)	1.04	0.99–1.09	0.152			
Tumor number	0.54	0.15–1.92	0.340			
Tumor size (cm)	1.50	0.84–2.66	0.168			
Total bilirubin (mg/dL)	1.58	0.50–5.04	0.437			
Serum albumin <36 g/L	0.27	0.12–0.63	0.002	0.91	0.30–2.76	0.866
Prothrombin activity (INR)	18.7	0.67–521	0.084			
Platelet count (K)	1.00	0.98–1.01	0.104			
Serum AFP (ng/mL)	1.00	0.99–1.01	0.057			
FIB-4 index >5.29	3.61	1.51–8.63	0.004	1.65	0.60–4.54	0.330
Previous treatment for HCC						
(no vs. yes)	2.96	0.99–8.79	0.051			
LS value ≥13.3 kPa by 2D-SWE	5.09	1.50–17.3	0.009	4.30	1.26–14.7	0.020
Antiviral therapy	0.42	0.18–0.98	0.045	0.65	0.25–1.69	0.378
Intrahepatic distant recurrence	1.65	0.64–4.23	0.301			
Local tumor progression	2.71	0.99–7.44	0.052			
Extrahepatic metastasis	9.24	3.52–19.3	<0.001	7.24	3.08–17.0	<0.001

Table 3. Cox survival analysis of the predictors of recurrence-free survival in 134 patients with 161 HCCs after RFA

Characteristic	Univariate HR	95% CI	p value	Multivariate HR	95% CI	p value
Gender (male)	0.70	0.41–1.18	0.179			
Age (per 1 year)	1.01	0.99–1.04	0.339			
Tumor number	1.05	0.69–1.61	0.812			
Tumor size (cm)	1.06	0.76–1.48	0.741			
Total bilirubin (mg/dL)	1.02	0.55–1.90	0.950			
Serum albumin <36 g/L	0.65	0.40–1.05	0.077			
Prothrombin activity (INR)	2.02	0.30–13.8	0.472			
Platelet count (K)	1.00	0.99–1.01	0.556			
Serum AFP (ng/mL)	1.00	0.99–1.01	0.820			
FIB-4 index >5.29	1.22	0.77–1.92	0.403			
Previous treatment for HCC						
(no vs. yes)	3.26	1.98–5.40	<0.001	3.98	1.79–4.95	<0.001
LS value ≥13.3 kPa by 2D-SWE	1.39	0.84–2.01	0.146			
Antiviral therapy	1.52	0.89–2.60	0.124			
Local tumor progression	4.54	2.50–8.25	<0.001	3.64	2.00–6.61	<0.001

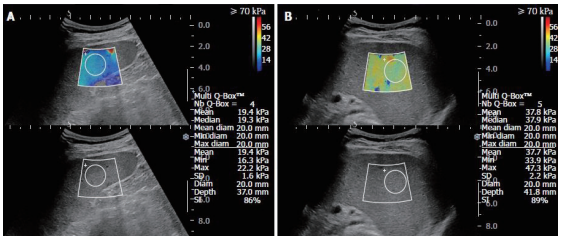
The estimated 1- and 3-year overall survival rates after RFA were 96.4 and 85.8%, respectively.
Cut-off value of LS 13.3 kPa:
3-year overall survival rates: 96.3 vs. 76.8% (hazard ratio = 4.30 [1.26–14.7]; p = 0.020).

The estimated 1- and 3-year recurrence-free survival rates after RFA were 63.4 and 37.6%, respectively; SWE-not significant

→ LS values measured by 2D-SWE was a significant predictive factor for overall survival after RFA for HCC.

Liver Cancer 2018;7:65–75

Spleen Stiffness(SS) Measurement by 2D-SWE (Examples)



a 50-year-old male patient with normal SS value: 19.4 kPa

a 57-year-old female patient with liver cirrhosis who underwent endoscopic variceal ligation (EVL); splenomegaly and increased SS value, 37.8 kPa

Cho YS, .., Sohn JH, et al. J Ultrasound Med 2019; 38:423–431

SS Measurement Using 2D-SWE: Predictors of Valid Measurement

Valid spleen stiffness values were obtained in 164 of the 310 patients (52.9 %).
Valid liver stiffness values were obtained in 292 of the 310 patients (94.2%).
* Valid results were defined as interquartile range divided by median (IQR/M) of less than 0.3, the index of validity used for TE

Table 1. Clinical Information for the Enrolled Patients

Parameter	Value
Male/female	174/136
Age, y	55.1 ± 12.5 (14–85)
Ascites	17
Disease etiology	
Fatty liver disease	46
Alcoholic liver disease	74
Chronic hepatitis B	99
Chronic hepatitis C	24
Rheumatic disease	38
Acute hepatopathy	7
Other	22

Data are expressed as number of patients and mean ± SD (range).

Table 2. Measured Patient Parameters

Parameter	Value
Body habitus	
Abdominal wall thickness, mm	17.0 ± 4.1 (8.0–31.1)
BMI, kg/m²	24.6 ± 4.1 (15.3–41.4)
Spleen size	
Longitudinal diameter, cm	10.0 ± 2.3 (3.5–19.2)
Short diameter, cm	3.8 ± 1.2 (1.2–79)
Splenic index	40.3 ± 20.9 (4.2–140.2)
Liver stiffness, kPa	11.7 ± 13.1 (3.3–99.1)

Data are expressed as mean ± SD (range).

* splenic index was calculated by multiplying the longitudinal and short diameters of the spleen.

Cho YS, .., Sohn JH, et al. J Ultrasound Med 2019; 38:423–431

Parameters of Success of Valid SS Measurement

Table 3. Univariate and Multivariate Analysis With Logistic Regression for the Prediction of Measurement Success of Valid Spleen Stiffness

Parameter	Univariate Analysis P	OR	95% CI	Multivariate Analysis P	OR	95% CI
BMI	.004	0.920	0.869–0.975			
Abdominal wall thickness	<.001	0.181	0.095–0.347	<.001	0.091	0.041–0.201
Spleen longitudinal diameter	<.001	1.736	1.478–2.039	<.001	2.108	1.703–2.609
Spleen short diameter	<.001	2.526	1.901–3.358			
Splenic index	<.001	1.066	1.046–1.087			
Liver stiffness	<.001	1.062	1.028–1.098			

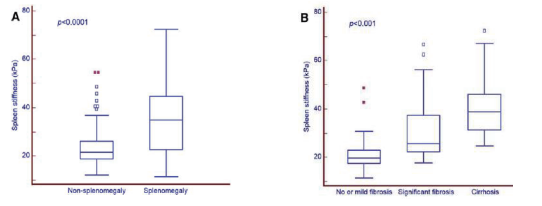
CI indicates confidence interval; and OR, odds ratio.

Parameters	Success rate (%)	p
Non-obese vs. obese	61.5 vs. 40.6	p<.001
Splenomegaly vs. no SM	80.0 vs. 41.6	p<.001
LC vs. no LC (F0-1, F2-3)	78.6 vs. 45.6, 51.8	p<.001

* Splenomegaly: Splenic index = a value of 44.4 cm² or greater

Cho YS, .., Sohn JH, et al. J Ultrasound Med 2019; 38:423–431

SS values :
According to spleen size and liver stiffness groups.



The no splenomegaly group: 23.7±8.7,
The splenomegaly group: 35.1±14.4 kPa.

F0, F1 fibrosis group: 20.4±5.7 (normal)
F2 and F3 fibrosis group: 31.9±13.4
F4 cirrhosis group: 40.2±10.5 kPa.

Cho YS, .., Sohn JH, et al. J Ultrasound Med 2019; 38:423–431

A Meta-analysis: Comparison of LS and SS for Esophageal Varices Diagnosis (LS<SS)

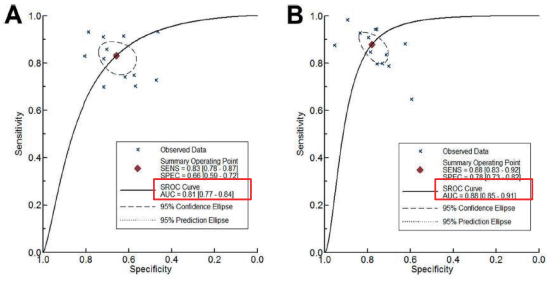


Fig 3. Summary receiver operating characteristic (SROC) curve of sensitivity versus specificity. (A) SROC curve of liver stiffness for prediction of any esophageal varices. (B) SROC curve of spleen stiffness for detecting the presence of esophageal varices.

PLoS One. 2016 Nov;11(11):e0165786.

Role of SS Measurement by 2D-SWE in Ruling Out the Presence of High-Risk Varices in Cirrhotic Patients

AUROC of LS and SS were 0.628 and 0.792, respectively. (SS> LS)

Table 3 Reliability of methods predicting the absence of high-risk varices (HRV)

Method	Spared UGE	HRV misclassification	Se	Sp	NPV	PPV
Patients with non-cholestatic liver disease						
LSM (cutoff value 27.5 kPa)	61.1% (33/54)	14.8% (8/54)	57.9% (11/19)	71.4% (25/35)	75.8% (25/33)	52.4% (11/21)
Baveno VI criteria	14.8% (8/54)	0% (0/19)	100% (19/19)	22.9% (8/27)	100% (8/8)	41.3% (19/46)
SSM (cutoff value 35.8 kPa)	48.9% (23/47)	4.3% (2/47)	88.9% (16/18)	72.4% (21/29)	91.3% (21/23)	66.7% (16/24)
Method	Spared UGE	HRV missing	Se	Sp	NPV	PPV
All patients						
LSM (cutoff value 22.5 kPa)	51.4% (36/70)	14.3% (10/70)	60% (15/25)	57.8% (26/45)	72.2% (26/36)	44.1% (15/34)
Baveno VI criteria	17.1% (12/70)	2.9% (2/70)	92% (23/25)	22.2% (10/45)	83.3% (10/12)	39.7% (23/58)
SSM (cutoff value 33.7 kPa)	40.6% (26/64)	3.1% (2/64)	91.7% (22/24)	60% (24/40)	92.3% (24/26)	57.9% (22/38)

LSM liver stiffness measurement, *SSM* spleen stiffness measurement, *UGE* upper gastrointestinal endoscopy, *AUROC* area under receiving operator characteristic, *Se* sensitivity, *Sp* specificity, *NPV* negative predictive value, *PPV* positive predictive value

Dig Dis Sci. 2019 Apr 15. doi: 10.1007/s10620-019-05616-4. [Epub ahead of print]

Summary: Take-home Messages

- 2D-SWE is a very useful non-invasive tool in evaluating liver fibrosis, portal hypertension, esophageal varices, and HCC.
- 2D-SWE is at least equal or slightly superior to TE in general (diagnostic performance, less limitation, etc.).
- However, large prospective multicenter studies are still limited and more clinical data are needed.

How to Improve Precision in Targeting Focal Lesion

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Image-guided percutaneous ablation is considered best in the treatment of early-stage hepatocellular carcinoma (HCC). Our 20-year outcomes show that ablation is a curative treatment and enables long-term survival. Since the ethanol injection period, we have had strong arguments regarding which treatment is superior for HCC, surgical resection or percutaneous ablation. A recent nationwide survey in Japan showed long-term survivals were similar between surgical resection and RFA. A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small HCC (SURF trial) recently demonstrated that the 3-year RFS of patients underwent surgery and RFA was 49.8%, 47.7%, respectively (hazard ration [HR] 0.96, 95% CI 0.72-1.28; *P*=0.793).

Various innovations have been introduced in the field of ablation, which would further improve outcomes. We developed a dedicated US transducer for puncture, with which we have performed RFA on 12,000 cases of liver tumors. A new version of this transducer with a better US image will be introduced into the market this year. Our dedicated procedure bed can keep a patient in an optimal position. Multimodality fusion imaging and US contrast agents are essential in our daily practice of ablation. We use these techniques in more than half of the cases. New-generation MWA systems incorporating antenna cooling and high-power generation have been receiving considerable attention. New-generation MWA can create a more predictable ablation zone, a larger ablation volume in a shorter procedure time. However, MWA antenna has some problems; it is difficult to insert into the liver. It cannot be seen clearly by US. It is easily broken. Further studies are needed from viewpoints of adverse events and long-term survival.

Incidentally, ablation is highly operator-dependent. Its skills and outcomes are very different from operator to operator. In order to disseminate skills and know-hows for ablation, we have held domestic training programs 12 times, with a total of 201 participants. We also have held international training programs six times, which were successfully completed with 91 participants in total. Programs are composed of comprehensive lectures, live demonstrations and case studies. Content of the lectures are overview of RFA, RFA devices, ultrasonography, and others. In the live demonstrations, RFA and new-generation MWA are performed on a wide variety of cases: cases of newly diagnosed cancer not difficult to ablate, tumors below the diaphragm requiring artificial ascites, in the caudate lobe, adjacent to the heart, a portal vein or hepatic vein, over 5 cm, more than five tumors, hepatic metastasis, etc. We demonstrate the importance of having appropriate patient posture, the usefulness of our original dedicated US transducer for interventional procedures and our dedicated procedure bed US-guided ablation, as well as ways to perform ablation under contrast-enhanced US guidance and with multimodality fusion imaging. In the case studies, difficult to ablate cases from participants' hospitals are presented and discussed. Many participants remarked on the benefit of being directly trained in an academic environment. Questionnaire surveys revealed overwhelmingly positive feedback from the participants. Our programs may be useful to provide opportunities to understand basic concepts and learn essential technical tips in ablation.

Sophisticated ablation, which is potentially curative, minimally invasive and easily repeatable for recurrence, would be superior to conventional surgery in some selected cases.

New Insight for Lower Abdomen and Kidney USG

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From Jan.1 2019, national health insurance was applied to the lower abdomen USG (appendix, small intestine, rectum, perineal area, inguinal area) and urinary USG (kidney, bladder, adrenal gland). Now we will discuss to these new issues about new applications and essential standard images about lower abdominal USG and urinary USG. The doctors who will perform ultrasonography have to obtain standard images and have to store the reading results of lower abdominal and urinary USG.

Keywords: Ultrasonography, Appendix, Intestine, Kidney urinary bladder

서 론

2019.2.1부터 하복부 초음파(충수.소장.대장.서혜부.직장.항문) 및 비뇨기(신장. 부산.방광) 초음파 요양급여 적용이 고시되었다. 진료의사의 의학적 판단에 따라 하복부나 비뇨기계에 질환이 의심되어 해부학적 이상을 진단하거나 경과관찰하기 위하여 의사가 직접 시행한 경우 건강보험 적용이 된다. 하복부 초음파는 급성 충수염을 포함한 장초음파와 신장 초음파, 골반 초음파를 일반적으로 통칭하나 이번 강의에서는 소장, 대장 충수의 초음파 소견과 신장 및 방광의 초음파에 대하여 다루도록 한다. 장초음파는 통상 간이나 췌장 등과 비교할 때 소화관은 관내에 존재하는 공기에 의한 반향(reverberation)과 길이가 매우 길고 구불구불하게 이어져 있어서 초음파 검사가 좀 더 어려운 부위이다. 그러나 급성 우하복부 통증을 호소하는 환자에서는 일차적으로 별다른 전처치 없이도 비교적 유용하게 이용할 수 있는 영상기법이기도 하다. 특히 초음파 검사는 급성 충수돌기염(acute appendicitis)의 진단과 다른 질환과의 감별 진단에 매우 유용하다.

신장 초음파역시도 신장염이나 신장결석 같은 급성 질환이나 암검진 등의 목적으로 다양하게 사용되고 있다.

I. 하복부 초음파 보험

1. 산정요건

획득해야 하는 표준 영상을 획득하고 검사의가 판독소견서를 작성하고 보관하여야 함. 단 제한초음파는 문제되는 부위 위주의 영상을 획득하고 판독소견서를 작성.보관하여야 함.

2. 표준영상

가) 충수; 상행결장 횡스캔, 상행결장 종스캔, 충수의 장축스캔, 충수의 횡축스캔 (충수가 안보일 경우 맹장 말단부 스캔)

나) 소장, 대장; 상장간막동정맥을 포함한 장간막 스캔, 회맹판 스캔, 복부의 사분면인 우상부, 우하부, 좌하부의 장이 각각 포함되는 스캔

다) 서혜부; 좌.우측 각각의 서혜부 횡스캔 좌.우 측 각각의 서혜부 종스캔

라) 직장.항문; 직장벽 5층이 포함되는 스캔, 항문의 하부스캔, 항문의 중부스캔, 항문의 상부스캔

3. 판독소견서

가) 등록번호, 성명, 생년월일 또는 나이, 성별, 검사명, 검사일시, 판독일시, 검사와 판독한 의사 (면허번호), 검사소견, 결론, 의료기관명

나) 충수; 충수 관찰 여부, 충수가 관찰된 경우 직경, 장벽의 비후 여부, 복수 유무, 충수식 유무, 농양 또는 액체저류 유무

다) 서혜부; 탈장 유무, 종괴 유무, 림프절 비대 여부

라) 직장; 직장벽의 종양 뮤무, 직장벽의 종양 침윤 정도, 직장벽 비후 유무, 주변림프절 비대 여부, 직장주위 종양 유무.

마) 항문; 치루 유무, 누관의 경로, 농양 유무, 종양 유무, 괄약근 손상 유무

II. 장초음파

1. 정상 장의 해부학

상행결장은 후복막에 고정되어 있고 거의 일정한 위치에 있으나 맹장은 사람에 따라 위치가 다양하게 위치해 골반강 내 혹은 상당히 상복부로 이동하여 위치하는 경우가 있어 주의를 요한다. 충수돌기는 횡맹관의 약 1-2 cm 하방, 즉 맹장의 후방중앙로 주행하는 경우가 가장 흔하다. 6-7 cm 정도로 주행하는 연동운동이 없는 끝이 막힌 관형구조물이다.

2. 장 초음파 검사법

A. 정상 소화관의 초음파상

정상 소화관은 초음파에서 5층으로 분리되어 보인다. 정상 장관 두께는 3~5mm이고 특징적인 소견과 연동운동 등으로 부위를 구분할 수 있다.

대장은 분변이 차 있어 더 복잡한 초음파음향을 보인다. 대장의 내용물은 분변과 기포 및 공기 층이 혼재된 음영과 반향을 보여 정상의 경우에서 장관벽이 잘 구분되어 보이지 않을 수도 있다. 분변은 내부에 미세 기포가 포함되어 있기 때문에 고에코로 보이지만 가스와는 달리 지저분한 후방음향을 동반하지는 않는다. 분변과 가스 음영 사이에 불규칙한 장관 내관으로 보이는 대장의 특징적인 구조물은 결장팽기(haustra)가 보인다. 충수돌기는 회장 말단과는 달리 연동운동이 없다.

3. 충수돌기 스캔법

위에 언급한 방법대로 상행결장을 찾은 다음 횡스캔을 이용하여 회맹관을 찾은 후 좀 더 하방의 충수돌기 시작부위를 찾는다. 대장의 분변이 많거나 가스가 많아 영상이 흐려질 때는 압박을 좀 더 하거나 후방 압박법, 체위변경 등의 방법을 사용해 본다. 점진적인 압박법 (graded compression technique)을 시행하여 장관과 지방층을 강압적으로 이동시키거나 압박하여 장관과의 거리를 줄여 주는 것이 해상도를 높여준다.

후방압박법을 시행하면 장관과의 거리를 좁힐 수 있고, 좌측누움위치 (left lateral decubitus 혹은 oblique position)을 취하게 되면 가스의 간섭을 줄일 수 있다. 고주파의 탐촉자를 사용하면 영상의 질을 좀 더 향상 시킬 수 있으나 환자가 피하지방이 많거나 충수가 깊게 위치한 경우는 낮은 주파(low frequency)의 탐촉자로 바꾸어 주는 것이 좋다.

또 한가지 방법은 환자가 가장 pain을 호소하는 Maximum tender point를 손가락으로 지적하게 한 후 그 부위에 염증이 있는 appendix를 먼저 찾은 후, 맹장과 연결되어 있는 끝을 가진 맹관 인지를 확인 하고, 맹장과 연결된 base를 확인하고, 그 상부의 IC Valve를 확인하는 방법이 있다.

III. 신장 초음파

1. 비뇨기 초음파 보험

1) 신장·부신; 신문(renal hilum)을 포함하는 좌·우신 각각의 관상면 스캔, 좌·우신 각각의 상부 횡스캔, 좌·우신 각각의 중간부 횡스캔, 좌·우신 각각의 하부 횡스캔

※ 부신 종괴가 있는 경우 종괴를 포함한 스캔

2) 방광; 방광 상부 횡스캔, 방광 중간부 횡스캔, 방광 경부 횡스캔, 방광 중간부 시상면 스캔

3) 판독내용

가) 신장·부신; 신장 실질의 에코, 신장의 크기, 신장의 국소병변(낭종, 고형종괴 등) 유무, 수신증 유무, 부신 이상 유무

나) 방광; 방광벽 비후 여부, 방광 종괴 유무, 방광 결석 유무

2. 신장 초음파의 해부학

신장은 후복강의 장기로 신피질과 신수질로 이루어진 신실질과 신배(calyx), 신우(pelvis), 신혈관과 결합조직 및 지방조직으로 구성된 신동(renal sinus)로 나뉘어 진다.

3. 신장의 스캔 방법

신장의 검사를 위해서는 특별한 전처치는 필요하지 않다. 다만 후복강내의 장기이기 때문에 앞쪽의 대장이나 위장관내의 의한 공기 음창의 방해를 받지 않도록 주의해야 한다. 그러므로 6-8시간의 금식을 권하며 배와위(supine position)가 기준 자세이고 경우에 따라 측와위나 복와위를 시행하기도 한다. 한 환자에서 앙와위, 와위, 전위, 복와위 등 다양한 자세로 바꾸어 검사하기도 한다. 같은 날 상부위장관 촬영이나 내시경 검사를 시행하는 경우는 초음파를 먼저 시행하는 것이 좋다. 우측 신장은 간의 우엽을 음창으로 사용하면 간실질의 에코와 간실질의 에코 차이를 비교하기 쉽다. 좌측 신장의 경우는 측와위 자세로 시행하는 것이 폐에 의해 가려진 좌측의 신장을 잘 관찰할 수 있다. 거동이 힘든 환자에서는 좌측 옆구리에 베개를 넣는 방법도 많이 이용된다.

신장 초음파 검사의 일반적인 적응증은 신장 크기의 측정, 요관 막힘의 진단, 신장 종괴의 유무 및 감별진단, 신실질의 해부학적 변화가 의심되는 경우, 신혈관을 평가하고자 할 때이고 절대적인 금기증은 거의 없는 장점이 있다.

신장 질환에서 초음파의 진단 정확도는 76-98%로 보고되고 있으며, 사용하기 편하여 환자의 순응도가 높고, 비침습적이며 방사선 해가 없고, 실시간 영상을 얻을 수 있다는 장점과 넓은 적응증으로 비교적 많이 쓰이는 진단modality이나 연조직간의 구분이 다른 modalities에 비하여 낮고 비특이적이며, 시야가 좁고, 시술자 의존적이며, 환자의 체형에 영향을 받는다는 단점이 있다.

성인에서 주로 3~5 MHz 곡선형 (convex) 탐촉자를 이용하여 좌우 신문부(renal hilum)이 포함되도록 신장의 장축 방향으로 시상면 스캔하여 최대 장경의 신장크기를 측정하고 탐촉자를 평행하게 움직여 앞쪽에서 뒤쪽으로 수직 장축의 단면을 얻는다. 이때 수신증의 동반여부나 신장 실질 뒤쪽의 근위 요관(proximal ureter)도 관찰해야 한다. 신문부가 포함된 장축 중심에서 탐촉자를 수직으로 돌려 평행하게 신장의 상극 (upper pole)에서 하극(lower pole)까지 스캔하여 횡축 단면 영상을 얻는다.

회색 초음파와 같은 순서로 색도플러 초음파를 시행하고 신혈관을 관찰한다. 신동이 보이는 시상면 색도플러 영상에서 엽간동맥(interlobar vessel)의 도플러 파형을 2회 이상 추출하여 저항지수(Resistive index;RI)를 측정한다.

방광 초음파는 소변을 참게 하거나 도뇨관을 통해 수액을 주입하여 방광을 확장 시킨 후에 시행해야 한다. 횡축으로 방광 천정부에서 방광 경부까지 관찰하고, 시상면에서 좌우 스캔하여 방광벽과 내부를 관찰한다. 잔뇨 검사 및 배뇨 후 변이를 보기 위해 배뇨 후 영상을 추가 하여 얻기도 한다. 이때 액체로 차 있는 방광은 artifact를 줄이기 위해 하모닉 영상을 추가하면 좋다.

4. 정상 신장 초음파 소견

초음파 검사에서 신피질의 에코는 간이나 비장의 에코보다 약간 낮거나 거의 비슷한 정도로 보인다. 지방간이 있는 환자에서 만성 신질환이 동반되어 있으면 정상처럼 보일 수도 있어 주의를 요한다. 신수질은 정상적으로 신피질과 비교하여 약간 낮은 에코로 구분되어 보인다. 정상 성인에서 대략 반반의 두께를 차지한다. 신수질-피

질의 구별은 환자의 체형, 초음파 탐촉자의 주파수, 그리고 환자의 수분 공급상태에 따라 다르게 나타난다. 신동(renal sinus)는 신장 중앙에서 지방조직으로 인해 고에코로 보이며 종단 스캔에서는 난원형으로 횡단 스캔에서는 원형으로 보인다. 이를 중심에코복합체(central echo complex)라고 부른다. 복합신배의 영향으로 양측 극부위는 저에코로 보이게 되어 종괴로 오인되기도 한다. 피질-수질 경계부를 따라 가는 궁상동맥(arcuate artery)은 밝은 에코를 보인다. 소신배는 정상적으로 잘 구분이 어려우나 대신배와 신우는 얇은 벽을 가진 무에코의 낭성 구조로 보인다.

초음파에서 신장의 크기는 일반적으로 종축의 길이가 9-12 cm, 횡축의 길이가 4-5 cm 정도이다 양측 신장의 크기 차이는 1.5-2 cm이내이다. 신장의 크기를 측정할 때 조심해야 하는 것은 신장의 가장 장축을 측정해야 하는 것이다 신장은 축은 회전에 다양한 변이가 있어 탐촉자의 방향을 적절히 기울여 신장의 가장 장축을 찾는 것이 중요하다.

5. 신장초음파의 한계점

양측 극(pole)에 RCC가 있을 경우 종괴가 저에코로 보여 진단이 어렵고, 소량의 지방을 함유한 Angiomyolipoma의 경우도 RCC와 감별이 어렵다. 또한 신실질 질환을 감별하는 데도 어려움이 있고 신기능을 평가하기도 어렵다. 초음파만으로는 특이도와 민감도에 한계가 있다.

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Present and Future of National Health Insurance System for USG: What Do We Need to Prepare for?

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In the past, the national insurance coverage of ultrasound examinations in South Korea was limited to cancer, heart and cerebrovascular diseases and rare incurable diseases.

As a Moon Jae-in Care, national medical insurance plan covered costs of abdomen ultrasonography in April. 2018.

Currently, the abdominal ultrasound starts with a budget of 250 billion won per year, and about 150,000 number of USG are made every month

In the process of negotiations with the government, it is estimated that the medical system will cost at least 2 trillion won for financial estimation after the classification of the behavior of the ultrasound.

Accordingly, the definition and number of actions of abdominal ultrasound were newly determined through reclassification to 52 division, But it seem to be very complex and unclear

The Korean association for the study of the liver should be recommends that accurate guidelines and set up to negotiate with the government, about the heath insurance review and assessment of abdominal ultrasonogram.

The aim of this presentation is to review the current changes of the present and anticipate the future of national health insurance system policy of abdominal ultrasound and think about what do we need to prepare for ?

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 3: Saturday, June 22, 2019 (09:00-10:00)
ROOM BC [2F] 203-204

USG Trainee Session (*K)

Chair:
Young Seok Kim (Soonchunhyang Univ.)

How to Utilize the Various Functions of USG Machine

Moon Young Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

Various Function of USG

- Doppler US
- CEUS
- Liver Package

Doppler US

Table 1. Alterations of haemodynamic parameter in cirrhosis found on Doppler ultrasound

	Cirrhosis with PH (compared with normal)	Accuracy and reproducibility	Clinical usefulness
Haemodynamic parameters			
PVV	Decreased	CV: 3–8%	PVV < 15 cm/s is associated with a sensitivity and a specificity of 88 and 96% for PH
PVF	Increased		
SVV	Increased	CV: 8%	SPI threshold of 3.0 predict presence of EV in 92% of patients
SVF	Increased		
HA resistance (RI, PI)	Increased or no change	–	Controversial
SA resistance (RI, PI)	Increased or no change	–	Controversial
RA resistance (RI, PI)	Increased	–	Renal PI > 1.14 is associated with poor prognosis. Higher than normal renal RI and PI have a high PPV (84–100%) for detection of severe PH.
SMA resistance (RI, PI)	Decreased	–	With liver dysfunction and cirrhosis progress, SMA resistance decrease while SMA flow increase.
SMA flow	Increased	–	
HV waveform	Flattened	CV: 7–10%	Monophasic wave form is associated with severe PH, with a sensitivity of 74% and a specificity of 95%.
DI of HV	Increased	CV: 7%	DI > 0.6 predict severe PH (HVPG > 12 mmHg) with a PPV of 91%

CV, coefficient of variation (calculated by dividing the standard deviation by the mean and multiplying by 100); DI, damping index; HA, hepatic artery; HV, hepatic vein; PH, portal hypertension; PVV, portal venous velocity; PVF, portal venous flow; RA, renal artery; SA, splenic artey; SMA, superior mesenteric artery; SPI, splenoportal index; SVF, splenic venous flow; SVV, splenic venous velocity; –, never been reported.

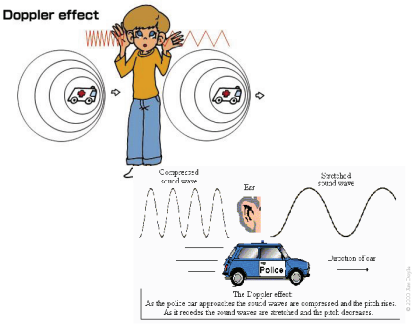
Baik SK. LI 2010

Doppler US

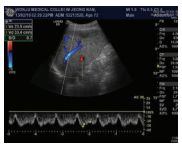
- Blood velocity
- Blood flow
- Vein waveform
- Arterial resistance

Doppler effect

Christian Andreas Doppler



Doppler US

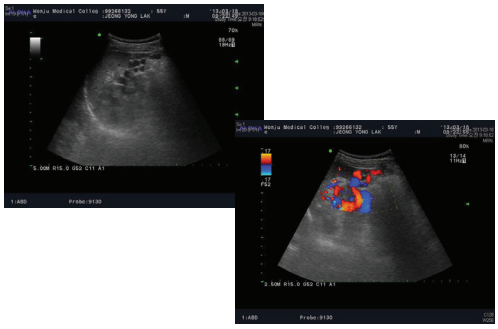


- Color Doppler
- Pulsed wave Doppler
- Continuous wave Doppler
- Power Doppler
- Spectral Doppler
- Duplex Doppler ultrasonography

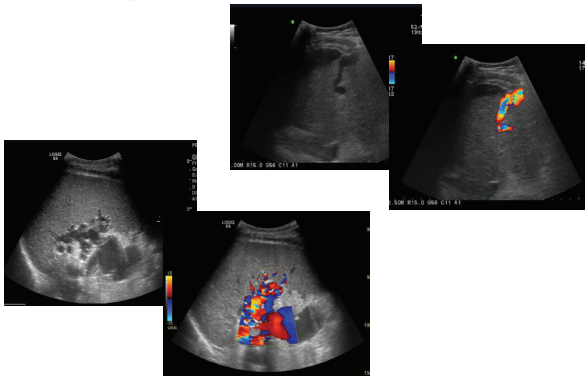
CDUS for PHT in CLD

- Porto-systemic abdominal collaterals
- Splenomegaly
- Portal vein, splenic vein and mesenteric vein dilatation
- Reduction of the respiratory variations of splenic and mesenteric vein diameters
- Hepatofugal flow (reversal of flow) in the portal vein system
- Reduction of portal vein blood velocity
- Subclinical ascites
-
- Congestion index of the portal vein
- flattening of Doppler hepatic vein waveform
- Eenal, splenic and SMA Doppler arterial impedance indexes

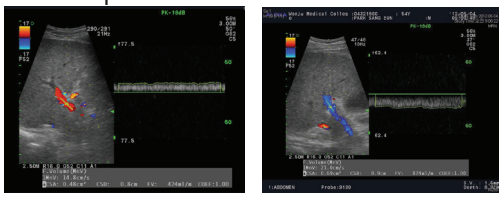
Porto-systemic abdominal collaterals



Porto-systemic abdominal collaterals



Reverse portal flow

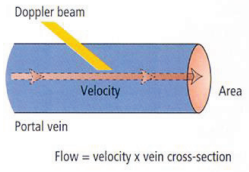


- Hepatofugal portal blood flow has been observed in **3 – 15%**
- in 228 pts with cirrhosis and PHT
- Child's C (15.4%) and B (12.5%) vs. Child's A (2.7%) (P < 0.02)
- Higher frequency of hepatic encephalopathy (21% vs. 7.2%; P < 0.05)
- Increase risk of variceal hemorrhage in 12-18months follow up (P < 0.02)

Gaiani S, et al. Gastroenterology 1991

Pulsed wave Doppler US - Vein

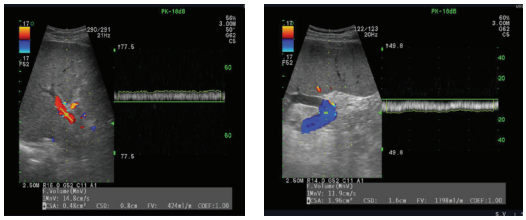
Blood velocity and flow



Portal vein

Splenic vein

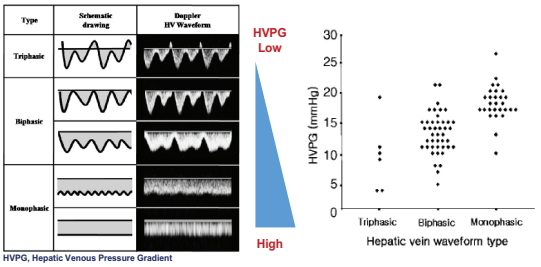
Portal & Splenic vein velocity & flow



PVV	↓	PVV < 15cm/s, ST 88% & SP 96% for PH
PVF	↑	?
SVV	↑	
SVF	↑	

Baik SK. Liver Int 2010

Doppler Hepatic Vein Waveform

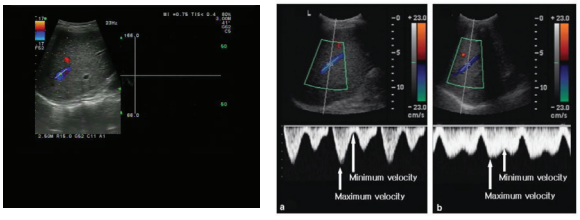


HVPG, Hepatic Venous Pressure Gradient

Mono-phasic HV for severe portal hypertension (HVPG>15mmHg)
: Odds ratio 28.8 / sensitivity 74 %, specificity of 95 %

Baik SK, et al. Radiology 2006

Damping Index: Quantification of HVW



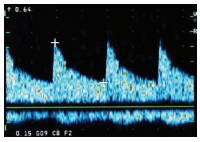
Kim MY, et al. Liver Int 2007

Pulsed wave Doppler US - Artery

Hepatic artery, splenic artery, renal artery

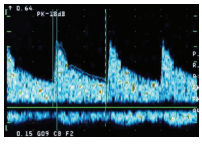
Resistive Index (RI)

$$\frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$$



Pulsatility Index (PI)

$$\frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{time averaged peak velocity}}$$



Baik SK. Liver Int 2010

superior mesenteric artery Doppler pulsatility index

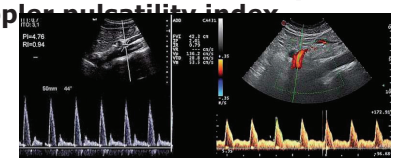


TABLE 2
Splanchnic and Systemic Hemodynamic Parameters in the Five Groups

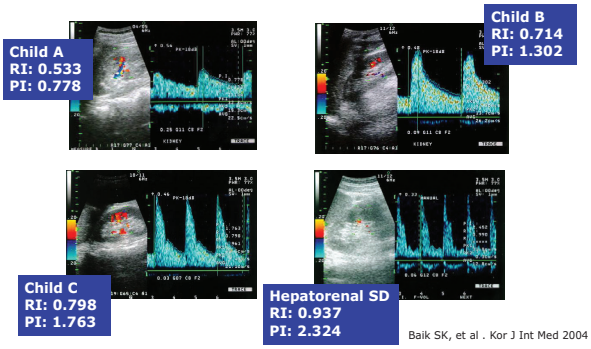
	Control Subjects	Group CH	Group NA	Group A	Group OLT	ANOVA
SMA-PI	3.42 ± 0.92*	3.28 ± 0.57*	2.71 ± 0.71*	2.40 ± 0.70*	2.77 ± 0.69*	$p < 0.0001$
SMA-RI	0.877 ± 0.054	0.873 ± 0.033	0.865 ± 0.034	0.841 ± 0.055	0.849 ± 0.046	p = NS
P vel (cm/s)	29.7 ± 7.9	33.4 ± 10.7	24.5 ± 6.0†	20.8 ± 4.9††‡	30.7 ± 10.9	$p < 0.0005$
P-CI	0.044 ± 0.017	0.038 ± 0.015	0.090 ± 0.039†	0.130 ± 0.047††‡	0.066 ± 0.036§	$p < 0.0001$
PFV (ml/min)	760 ± 247¶	819 ± 455¶	926 ± 344¶‖	948 ± 392‖	1168 ± 538	$p < 0.0005$
MAP (mm Hg)	100.8 ± 11.2	95.0 ± 11.7	97.4 ± 9.5	87.6 ± 10.4***	109.6 ± 11.0††	$p < 0.0002$
HR (beats/min)	65.9 ± 9.4¶	67.6 ± 10.1¶	68.8 ± 9.5¶	70.7 ± 8.8	77.6 ± 9.8	$p < 0.001$

* See fig. 1; †$p < 0.01$ *vs* C/CH/OLT; ‡$p < 0.01$ *vs* NA; §$p < 0.01$ *vs* C/CH; ¶$p < 0.05$ *vs* OLT; ‖$p < 0.05$ *vs* C; **$p < 0.01$ *vs* C; ††$p < 0.01$ *vs* C/CH/NA/A. Group C, controls; group CH, patients with chronic hepatitis; group NA, patients with liver cirrhosis free from ascites; group A, patients with liver cirrhosis with ascites; group OLT, liver transplant recipients; K-W, Kruskal Wallis analysis; SMA superior mesenteric artery; RI, resistance index; PI, pulsatility index; P-vel, portal vein mean of maximmun velocities; P-CI, portal vein congestion index (see text), PFV, portal flow volume; MAP, mean arterial pressure; HR, heart rate.

Piscaglia F, Am J Gastroenterol 1998

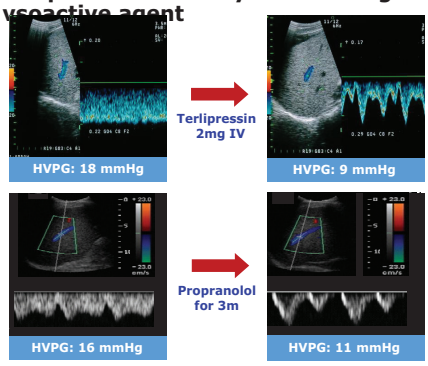
Doppler US

Normal and abnormal resistance by RI and PI



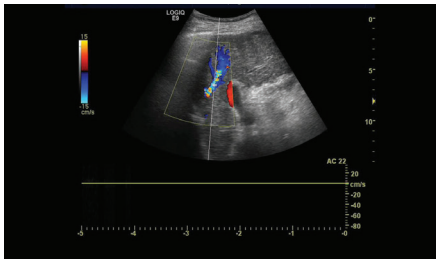
Baik SK, et al . Kor J Int Med 2004

HVW represents hemodynamic change by vasoactive agent

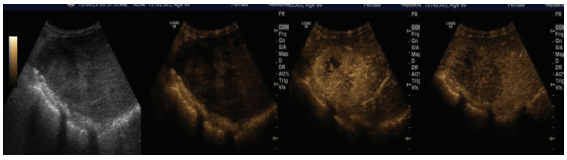


Baik SK, et al. Radiology 2006
Kim MY, et al. Liver Int 2007

Hepatic Vein Waveform



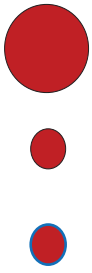
What is CEUS ?



Grey scale US | Pre-injection | Arterial phase | Late phase

동영상

US Contrast Agent(UCA)



FREE GAS BUBBLES

모세혈관을 통과할 수 없는 크기의 기포
자작의 기포는 이 분류 입니다.

ENCAPSULATED AIR BUBBLES

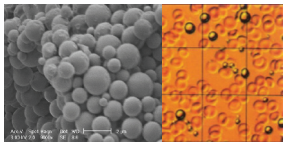
제1세대
모세혈관을 통과할 수 있는 정도의 크기로、껍질(쉘)을 갖고 있지 않은 기포。
Levovist

LOW SOLUBILITY GAS BUBBLES

제2세대
모세혈관을 통과 할 수 있는 정도의 크기로 、껍질(쉘)을 가지는 기포。
SonoVue, Sonozoid.

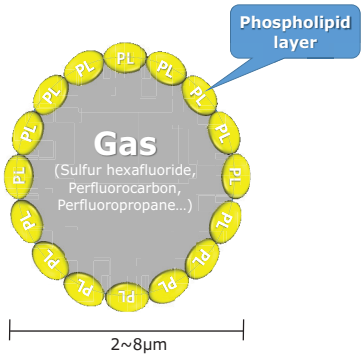
US Contrast Agent(UCA)

Microbubble (ø2-8μm)
>Small sphere of gas
>2nd: Phospholipid layer for stabilization in blood
>Low MI imaging:↑stability, ↓solubility

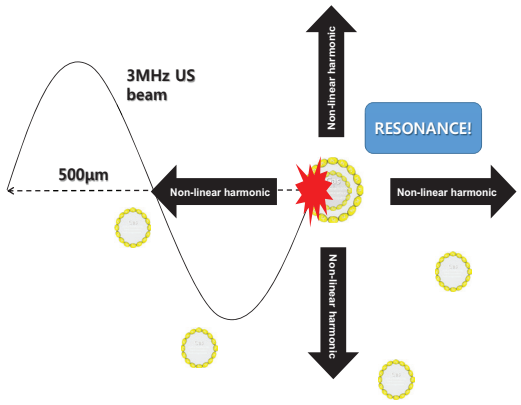


Margaret A et al. Ultrasonics 2006

Structure of 2nd UCA

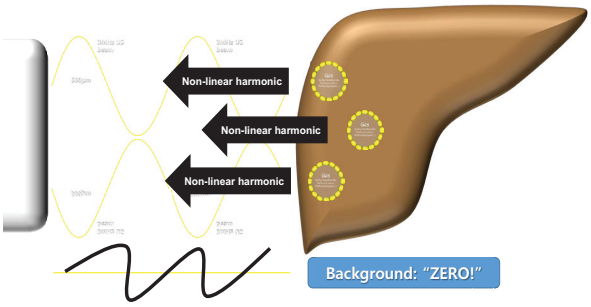


Mechanism of CEUS imaging



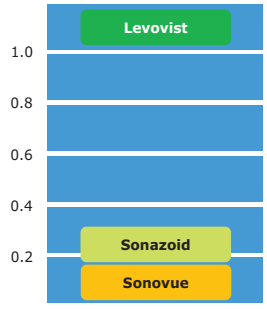
Pulse Inversion Harmonic

Basic principle: Detection of USCA



UCAs – Mechanical index (MI)

MI value



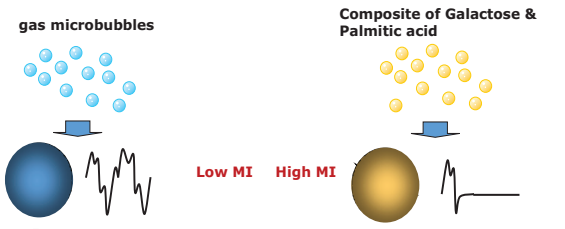
1st

The image by destruction of bubble
Intermittent imaging

2nd

The image by resonance behavior of bubble
Real time imaging

2nd generation vs. 1st generation UCA



Harmonic Mode	Imaging method	Doppler Mode
• High Real-time imaging • Observe organ continuously • Higher resolution • Insensitive to other mobilizing organs (eg, Heart)		As CE disappears shortly; • No continuous imaging • Low Real-time imaging • Sensitive to mobilizing organs • Low resolution

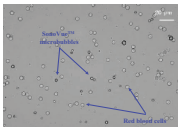
Various UCAs

Products	Manufacturer	Inner gas	Outer shell	Mean size (μm)
1st generation USCA				
Levovist®	Bayer (Schering)	Air	Bubbles stick to galactose & thin palmitic acid shell	2-3
2nd generation USCA				
SonoVue®	Bracco	Sulfur hexafluoride	Phospholipid	2.5
Sonazoid®	GE (Amersham)	Undisclosed perfluorcarbon	Lipid	3.0

Contrast enhanced US(CEUS)

SonoVue®

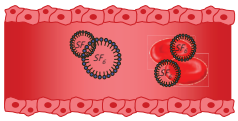
- 2nd generation ultrasound contrast agent, Bracco, 2001
- made of sulfur hexafluoride and phospholipids
- Characterized by a microbubble structure consisting of gas bubbles stabilized by a shell
- SonoVue® microbubbles (2.5 microns) cross the pulmonary barrier and circulate within the blood vessels.



M.Schneider, et al. Investigative Radiology 1995

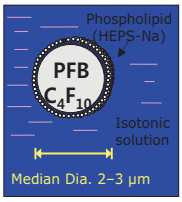
SonoVue®

- Due to the bubble size, SonoVue® is a pure blood pool agent.
- It doesn't extravasate into the interstitial space (vascular tracer)
- Strongly increase the US backscatter and therefore are useful in the enhancement of echogenicity for the assessment of blood flow and vasculature, focal liver lesions

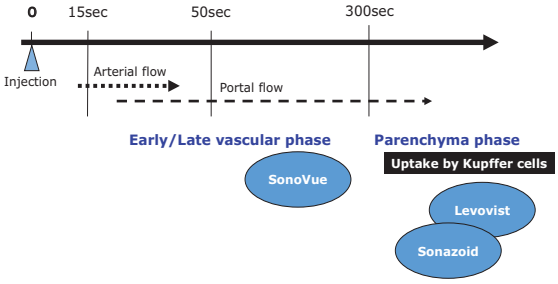


Sonazoid®

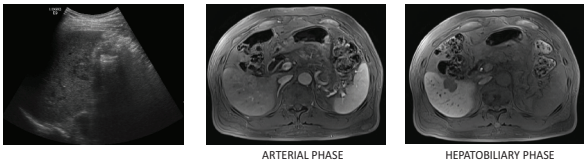
- perflubutane microbubbles
- suspended with 2 mL of attached water for injection.
- Usually, once for an adult, 0.015 mL/kg as suspension is administered intravenously.
- At late phase, phagocytosis by Kupffer cell – **Kupffer image**
- for Focal Liver Lesions in Ultrasonography

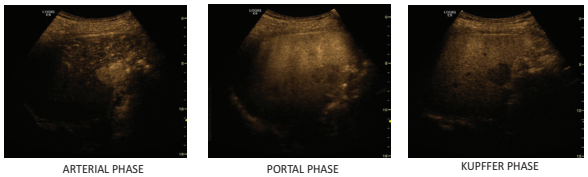


UCAs hemodynamic in Liver

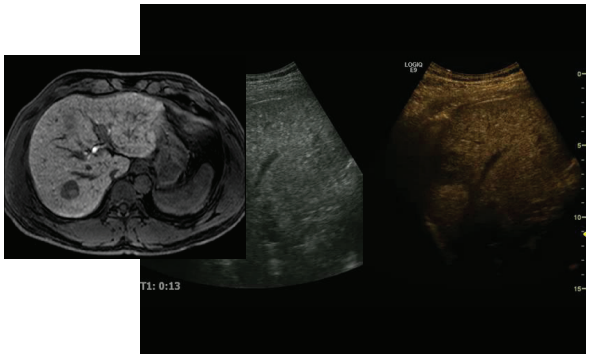


Mass contrast enhanced US(Sonazoid)





HCC-sonazoid



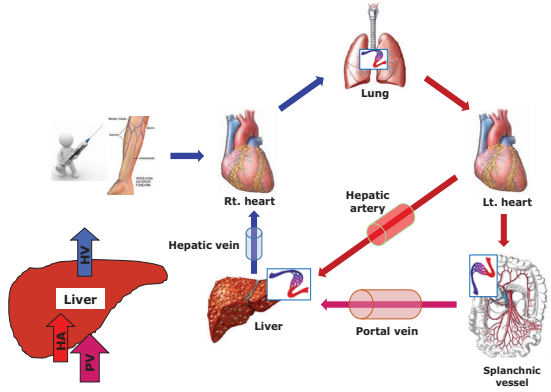
Diagnosis
- comparison with CT scan -

- CEUS now almost equals CECT
  (in some instances, CEUS exceeds CT in accuracy)
- Real time nature of CEUS : reveals important rapid flow phenomena
  (CT, with its intermittent imaging, sometimes misses these)
- Partly, also the persistence of microbubbles beyond the large vessel enhancement period(the late phase) provides a marker for the sinusoidal space; lesions that lack this vascular space, notably metastases, appear as late phase defects (sinusoidal phase)
- The origin of this late phase suggests mechanisms include sinusoid pooling and RES/Kupffer cells uptake

2nd UCA's Safety

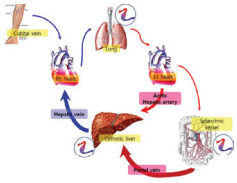
- Not nephrotoxic and do not interact with the thyroid
- Not necessary of renal function test before administration
- Very safe with a low incidence of side effects

Hemodynamic in cirrhosis



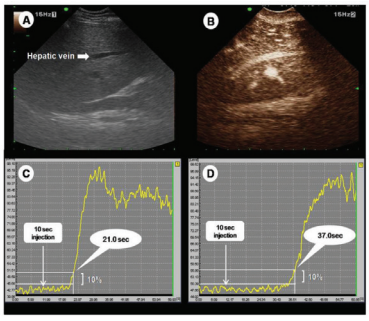
Hepatic Vein Arrival Time (HVAT) (sec)

- **Time until microbubble contrast arrive at hepatic vein after injection of microbubble contrast**
- **Shortening in advanced fibrosis and cirrhosis due to abundant shunts formation**



Kim MY, et al. Hepatology 2012

Hepatic Vein Arrival Time (HVAT) (sec)



Kim MY, et al. Hepatology 2012

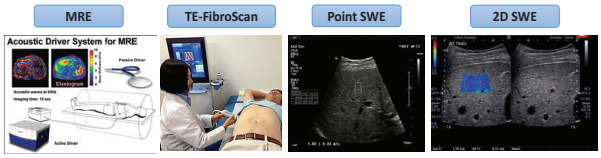
Shortening of HVAT – formation of collaterals and shunts

- **Intrahepatic sinusoidal remodeling**
  - ✓Capillarization and arterialization
- **New angiogenesis**
  - Vascular endothelial growth factor (VEGF)
  - Platelet derived growth factor (PDGF)
  - Placental growth factor (PlGF)
- **Opening of pre-existing vessels**

Liver Package for Diffuse Liver Disease

- Shear Wave Elastography
- Shear Wave Dispersion
- Attenuation Image

Commercialized Abdominal Elastography Equipment



- ✓ Non invasive method
- ✓ Imaging depth/more global look at tissue
- ✓ Fat quantification
- ✓ Expensive
- ✓ Long exam time

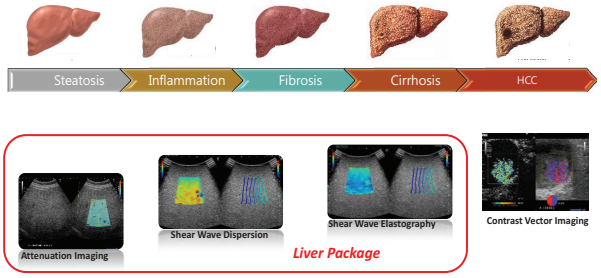
- ✓ Non invasive method, but no 2D image
- ✓ 10 times measurement
- ✓ Limited in obesity and ascites

- ✓ Non invasive method and cost effective
- ✓ 2D image + Liver stiffness measurement
- ✓ Easy & short exam time
- ✓ Better spatial resolution

- ✓ No Elasto color map
- ✓ Small ROI

- ✓ Elasto color map
- ✓ Large ROI

Liver Package



Osna et al. Alcohol Research: Current Reviews 2017:38(2)

Liver Package for Diffuse Liver Disease

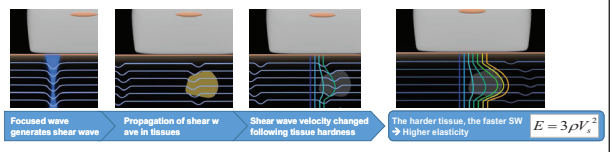
Liver Assessment

- Fibrosis → Elastography
- Steatosis → MRI or Biopsy
- Inflammation → Biopsy

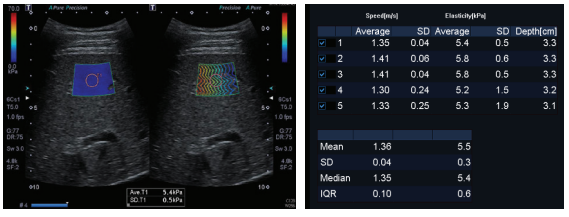
- **Shear Wave** quantifies tissue stiffness that is correlated with fibrosis.
- **Attenuation Imaging** quantifies tissue attenuation that is correlated with fat infiltration.
- **Dispersion Imaging** quantifies frequency dispersion that is correlated with viscosity related to necro-inflammation.

Shear Wave Elastography

- Deformation of tissue through strong push pulse, shear wave is generated.
- Shear wave propagates faster in stiffer tissue.
- Shear wave propagation (phase velocity) is traced.
  - ✓Plotting shear wave propagation with same interval.
- Elasticity (kPa) can be calculated through shear wave speed (m/s)



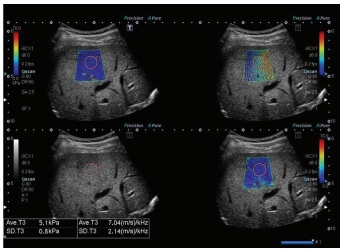
Shear Wave Elastography



	Speed[m/s] Average	SD	Elasticity[kPa] Average	SD	Depth[cm]
1	1.35	0.04	5.4	0.5	3.3
2	1.41	0.06	5.8	0.6	3.3
3	1.41	0.04	5.8	0.5	3.3
4	1.30	0.24	5.2	1.5	3.2
5	1.33	0.25	5.3	1.9	3.1
Mean	1.36		5.5		
SD	0.04		0.3		
Median	1.35		5.4		
IQR	0.10		0.6		

Shear Wave Dispersion

- Visualizing and measuring ***frequency dispersion*** of shear wave propagation.
- Viscosity ↑ (inflammation, steatosis, circulation disorder etc), Dispersion ↑
- ***Quantification of Dispersion*** [(m/s)/kHz)] allows ***estimation of liver viscosity***.



Liver Package for Diffuse Liver Disease

Preliminary Clinical Evaluation

Acute hepatitis : **"Viscosity" > "Elasticity"**
Cirrhosis model : **"Elasticity" > "Viscosity"**

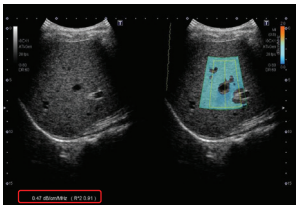
↓

Elasticity → Fibrosis
Viscosity → Necrosis & Inflammation of hepatocyte

Sugimoto K, Moriyasu F, et al. Kanzo 2017;58(9):536-539

Attenuation Imaging

- Quantify degree of attenuation by attenuation coefficient (dB/cm/MHz)
- Potential clinical benefit as an indicator of liver steatosis.

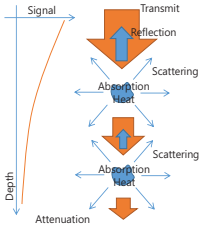


Attenuation Imaging

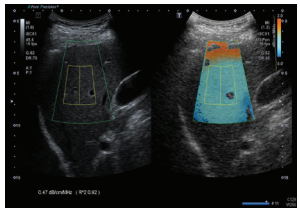
- The ultrasound waves in the body are attenuated by acoustic scattering, reflection, and absorption (heat).
- Attenuation is frequency-dependents.

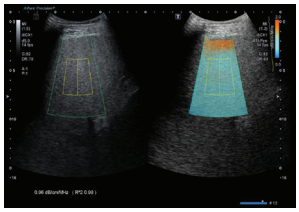
Tissue	Attenuation Coefficient (dB/cm/MHz)
Blood	0.12 - 0.16
Liver	0.45 - 0.52
Fat	0.6 - 1.0
Muscle	0.57 - 2

Duck FA. (1990). *Physical Properties o f Tissue: A Comprehensive Review*

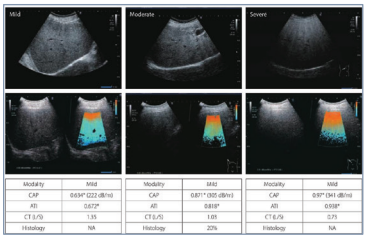


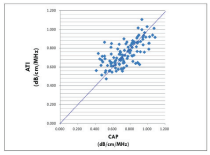
ATI – Hepatic steatosis





ATI study with CAP





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JSUM 2017

Summary

- US has some limitations in accuracy so it has been mailly applied as screening test in the past
- However, US is one of the most promising non-invasive diagnostic tool for the detection of cirrhosis/portal hypertension and malignancy
- Various new technology of US is upcoming beyond Doppler US including elastography, attenuation image, viscosity, contrast US
- New horizon of Image biomarkers
- Early try, early adapt, early research

Basic Liver Scanning and Key Findings

Jeong Eun Song

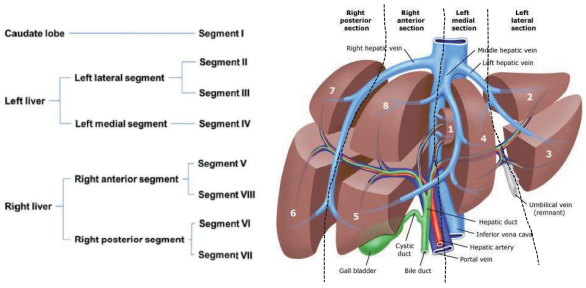
Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, Korea

Contents

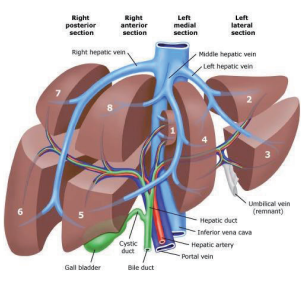
- **Liver Anatomy**
- Basic Liver scanning
- Key Findings in USG

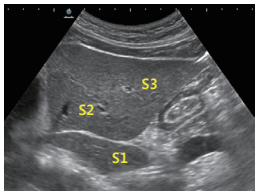
Liver anatomy – Couinaud segmentation

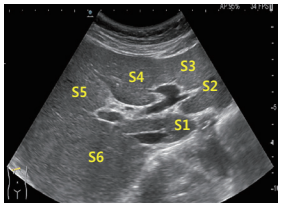
- Hepatic veins : 구역의 경계를 주행
- Portal veins : 구역의 중심을 주행



초음파 화면의 이해 : 3차원적 구조의 2차원적 이미지화

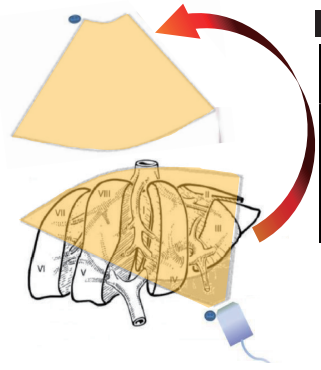




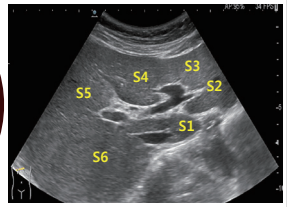


박하나, 간의 정상 구조 및 초음파 기본 스캔법, 2018 제2회 전임의, 전공의를 위한 간질환 연수강좌 및 초음파 Hand-on

초음파 화면의 이해 : 3차원적 구조의 2차원적 이미지화



Probe에서 가까운 구조가 화면의 상부



Probe에서 먼 구조가 화면의 하부

횡스캔 (Transverse scan)

박하나, 간의 정상 구조 및 초음파 기본 스캔법, 2018 제2회 전임의, 전공의를 위한 간질환 연수강좌 및 초음파 Hand-on

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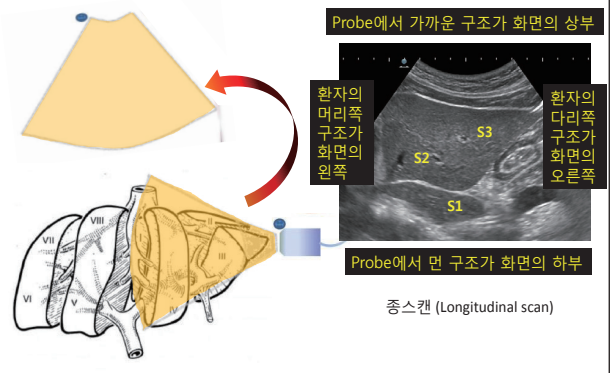

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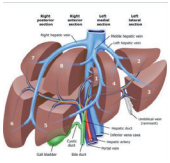
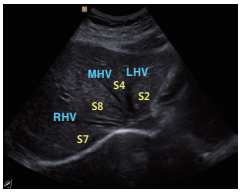
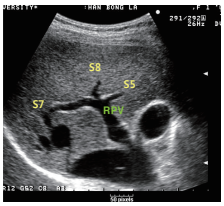
간 구역 구분의 Landmark

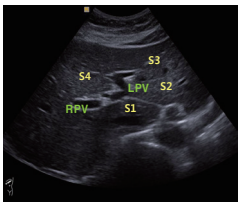


- Hepatic veins

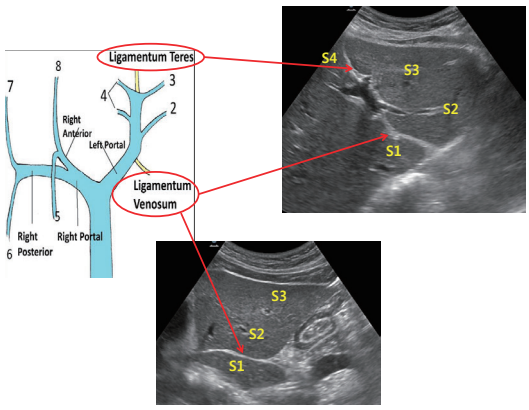


- Portal veins





간 구역 구분의 Landmark

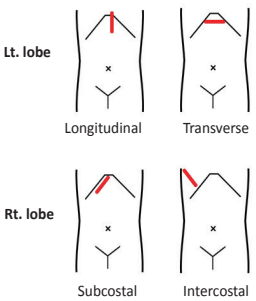


Contents

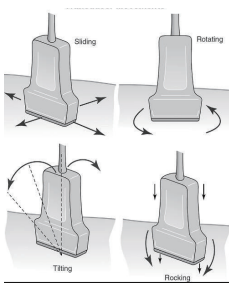
- Liver Anatomy
- **Basic Liver scanning**
- Key Findings in USG

탐촉자 스캔 조작 방법

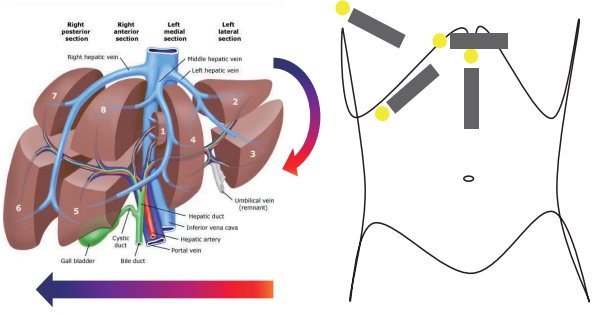
- 탐촉자 위치



- 탐촉자 움직임



일정한 순서로, 다양한 스캔법을 이용



Blind Spot

상복부 초음파 표준영상

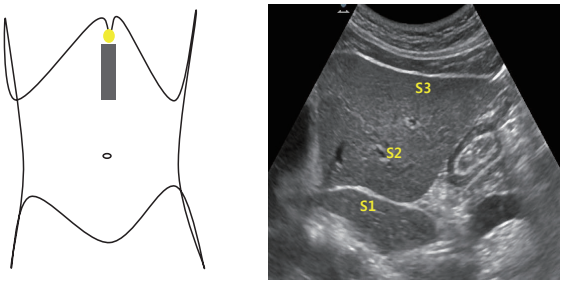
보건복지부 고시 제2018-66호

- Liver
  - Lt. subcostal
    - 1) 간좌엽의 종스캔
    - 2) 간좌엽의 횡스캔
  - Rt. subcostal
    - 3) 간정맥의 늑간하스캔
    - 4) 좌우간문맥 분기점의 횡스캔 (정밀)
    - 5) 간우엽의 상부
    - 6) 간우엽의 횡스캔
  - Rt. intercostal
    - 7) 우간문맥을 포함한 간우엽의 늑간스캔 (정밀)
    - 8) 우간정맥을 포함한 간우엽의 늑간스캔 (정밀)
  - Hepatorenal contrast
    - 9) 우간하부와 우측신장피질의 관상면 스캔

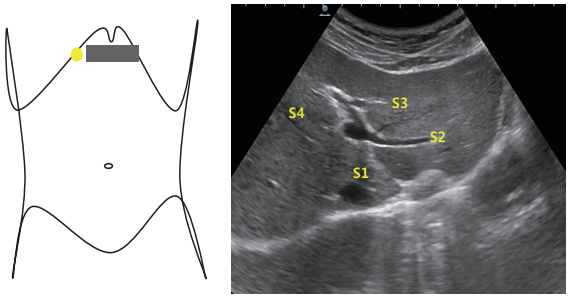
표준영상을 기본으로 초음파 이미지를 검사 결과로 남겨야 하지만,

초음파 검사의 기본적인 성격은, **Live !**

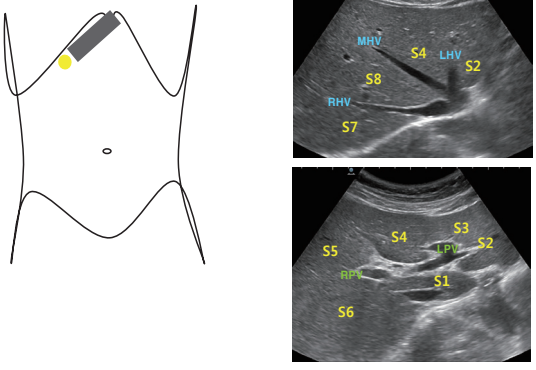
1. 간좌엽의 종단 스캔



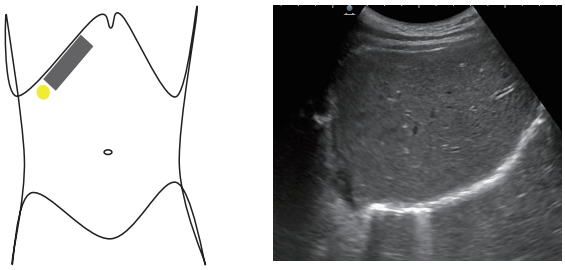
2. 간좌엽의 횡단 스캔



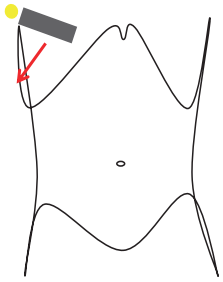
3. 간정맥의 늑간하스캔 & 4. 좌우간문맥 분기점의 횡스캔

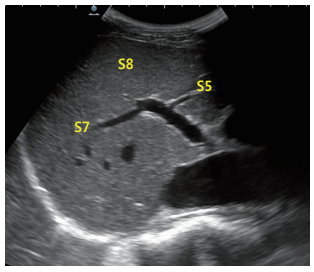


5. 간우엽의 상부 & 6. 간우엽의 횡스캔

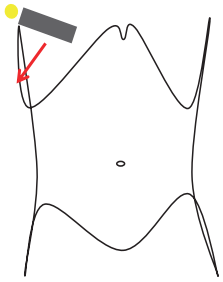


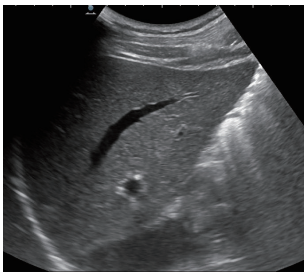
7. 우간문맥을 포함한 간우엽의 늑간스캔



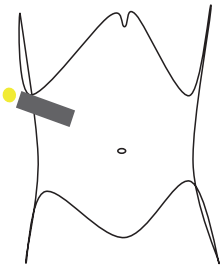


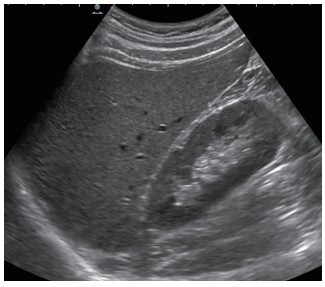
8. 우간정맥을 포함한 간우엽의 늑간스캔





9. 우간하부와 우측신장피질의 관상면 스캔





Contents

- Liver Anatomy
- Basic Liver scanning
- **Key Findings in USG**
  - **Diffuse liver disease**
  - **Focal liver lesions**

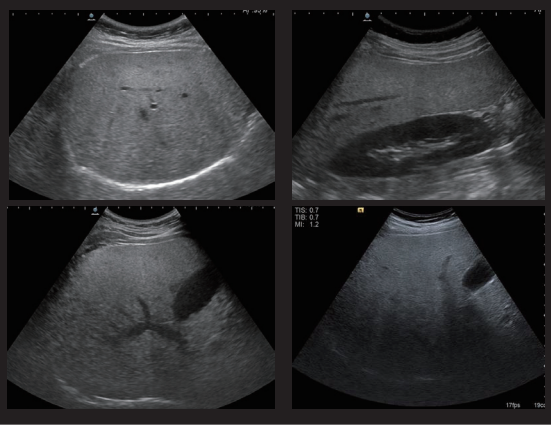
Diffuse Liver Disease

- **Fatty liver**
- **Chronic liver disease – Liver cirrhosis**

Fatty liver

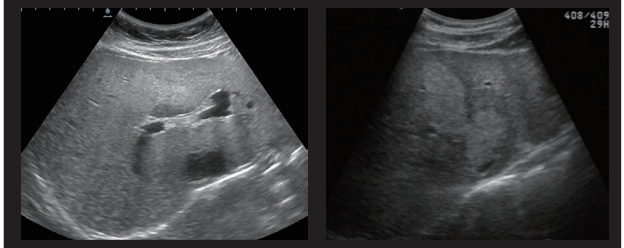
- **Bright Liver**
  - 신장 (hepatorenal contrast) 및 비장 (hepatosplenic contrast) 에 비해 간실질의 에코가 높아짐
- **Vessel blurring**
  - 간실질 에코의 증가로 인해 간문맥의 벽에코가 보이지 않음
- **Deep attenuation**
  - 음향 감쇠의 증가로 인해 횡격막 같은 심부 구조물이 보이지 않거나 희미하게 보임

Fatty liver



Focal lesion in Fatty liver

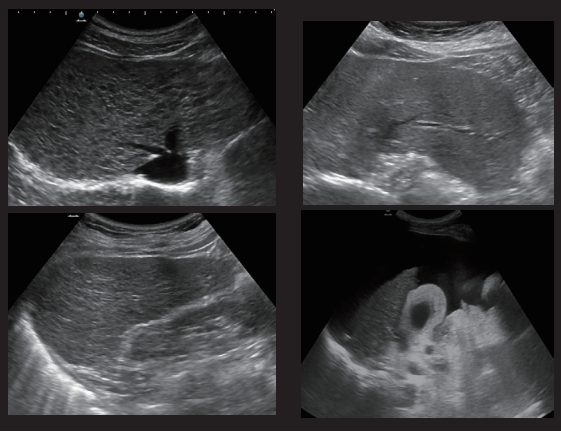
- Focal fat sparing
- Focal fat deposition



Chronic liver disease – Liver cirrhosis

- **Echo patter of liver parenchyme**
  - coarse ~ meshwork pattern
  - fatty fibrotic pattern
- **Liver Surface irregularity**
  - slightly irregular ~ nodular
- **Change of liver contour**
  - 간엽 끝이 둔화
  - 간좌엽 및 caudate lobe 비대
- **Extrahepatic change (Liver cirrhosis)**
  - Splenomegaly, ascites, GB wall edema, collateral circulation

Liver cirrhosis

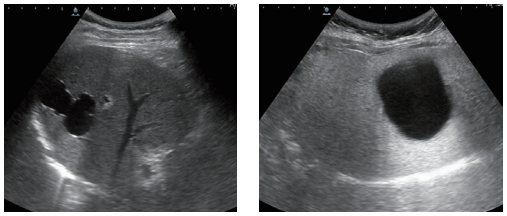


Focal liver lesions

- **Liver cyst**
- **Hemangioma**
- **Hepatocellular carcinoma**

Liver cyst

- **Anechogenicity (무에코)**
- **Well-defined capsule (경계가 명확한 피막)**
- **Posterior enhancement (후방음영증가)**

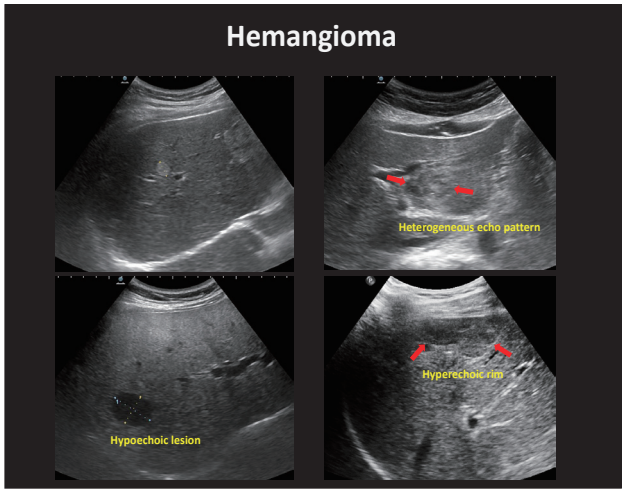


Hemangioma

- **전형적인 초음파 소견**
  - 분명한 경계와 균일한 고에코
  - 간혹 후방음향증강 소견이 동반

- **비전형적인 초음파 소견**
  - 불균질한 종괴 내부 에코
  - 고에코의 테두리 (hyperechoic rim)가 동반
  - 지방간에서는 저에코의 병변으로 보이도 함

* 비전형적인 초음파 소견은 지방간이나 만성 간염, 간경변증 등 주위 간실질 에코가 증가하는 경우에 흔히 관찰됨. 악성 간종양과의 감별이 어려운 경우가 흔함.

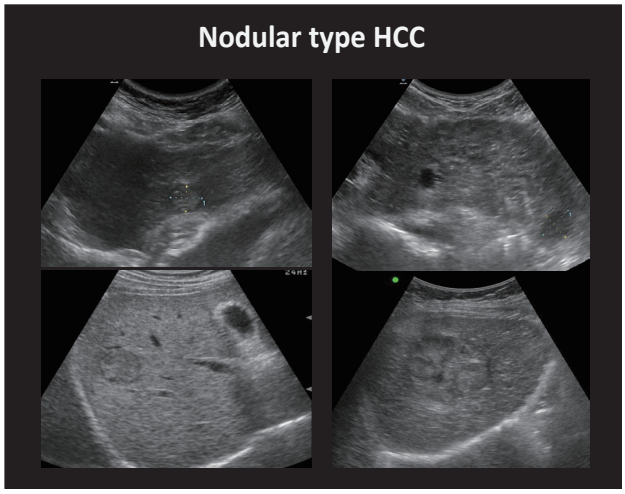


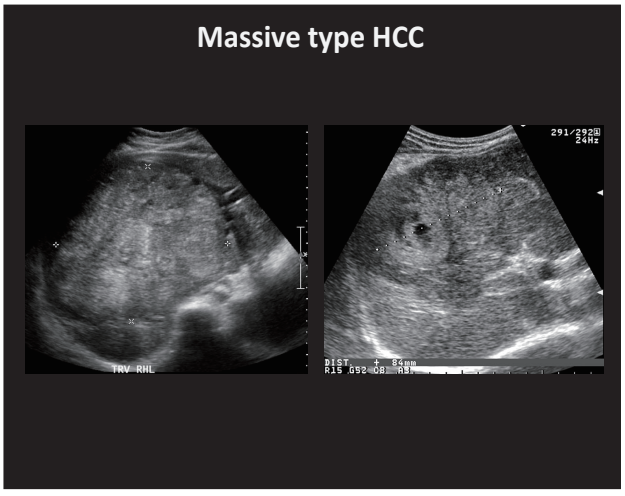
Hepatocellular carcinoma

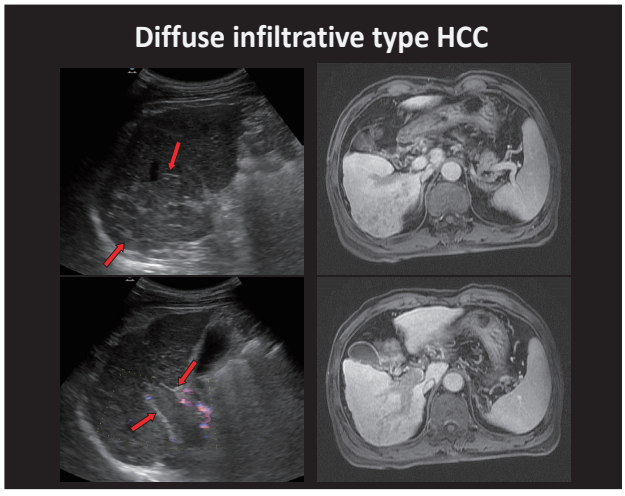
- **동반질환 유무 확인 (만성 B형 간염, 만성 C형 간염, 간경변증 등)**

- **다양한 초음파 소견**
  - **내부 에코 : 저에코 , 고에코, 모자이크 양상 (> 4cm)**
  - **변연저에코대 (Halo sign)**
  - **측방음영**
  - **Hump sign**

- **형태에 따른 분류**
  - **결절형 (nodular)**
  - **괴상형 (massive)**
  - **미만형 (diffuse infiltrative)**







Pancreatobiliary USG Scanning Made Easy

Soon Sun Kim

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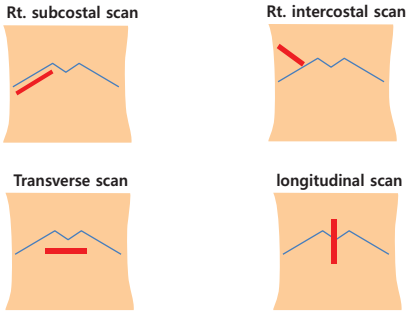
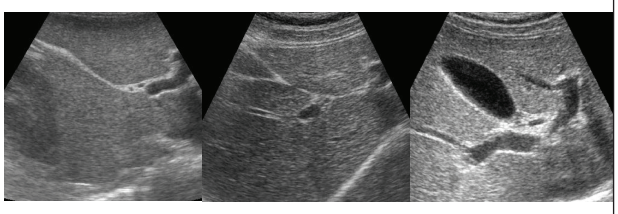
상복부 초음파의 기본 스캔



담낭 초음파 스캔

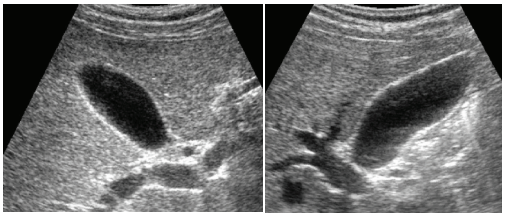
Location of GB

- Main interlobar fissure
  (GB fossa between right & left lobe)

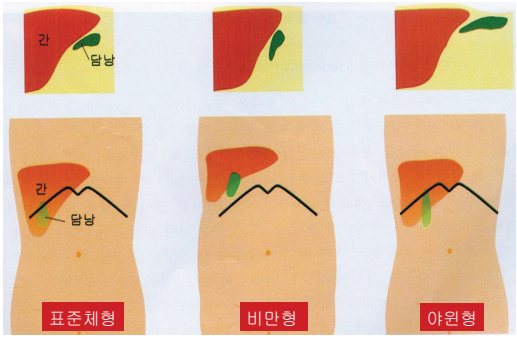


Normal GB

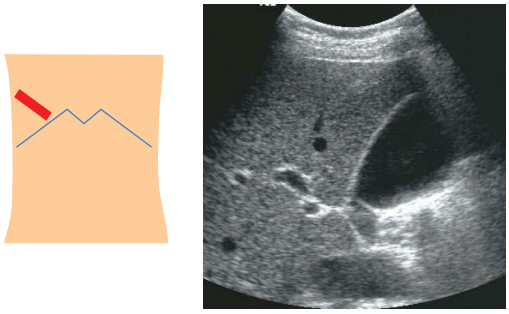
- 장경 10 cm 이하, 단경 5 cm 이하, 용적 100-160 ml
- 담낭벽두께: 공복시 2-3 mm, 식후 4-7 mm



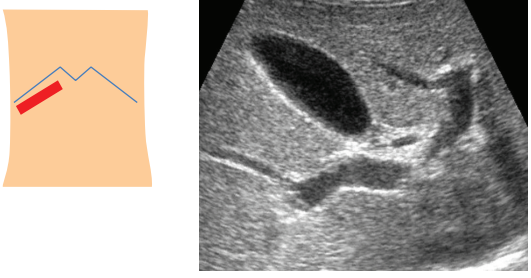
체형에 따른 담낭과 간의 위치관계



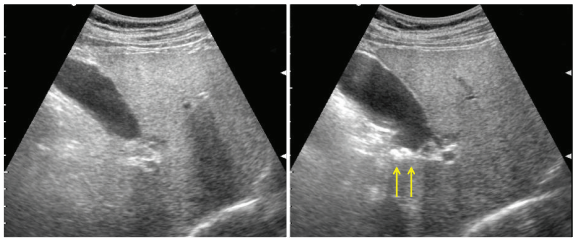
Rt. intercostal scan



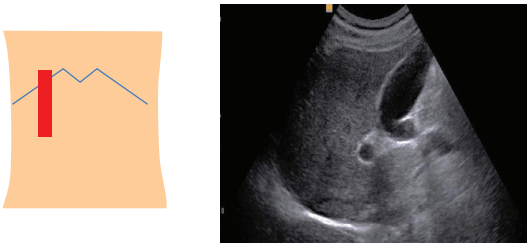
Rt subcostal Scan



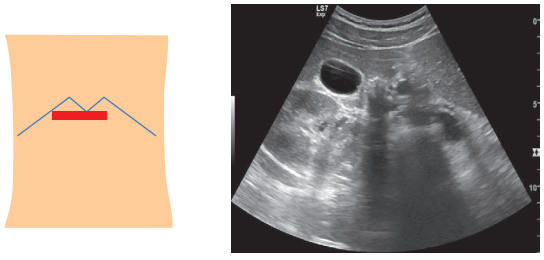
Lt lateral decubitus position



Rt. longitudinal scan



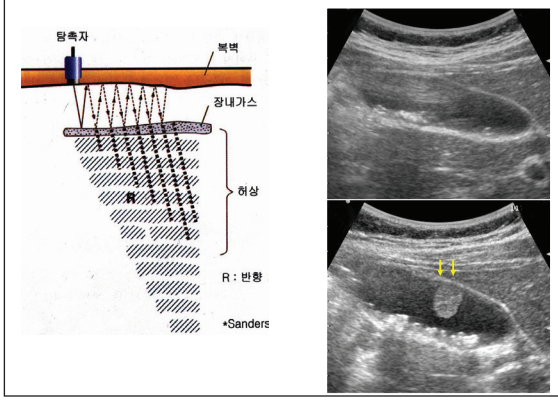
Rt. transverse scan



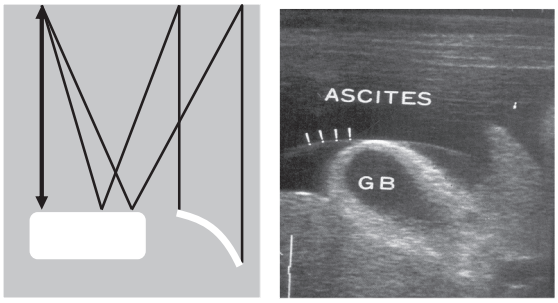
Artifacts of GB

- 반향허상 (reverberation artifact)
- 측엽허상 (side lobe artifact)
- 단면상 두께에 의한 허상(slice-thickness artifact)

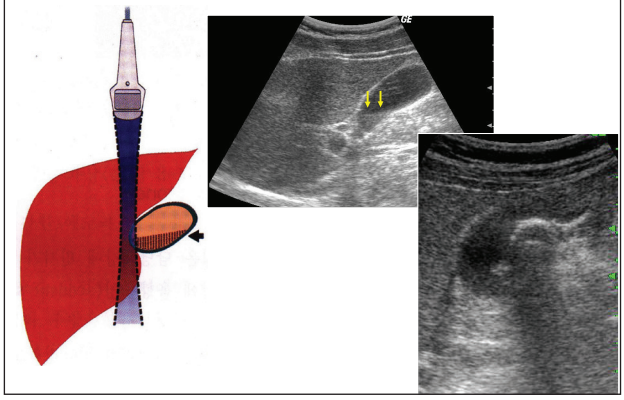
Reverberation artifact



Side lobe artifact

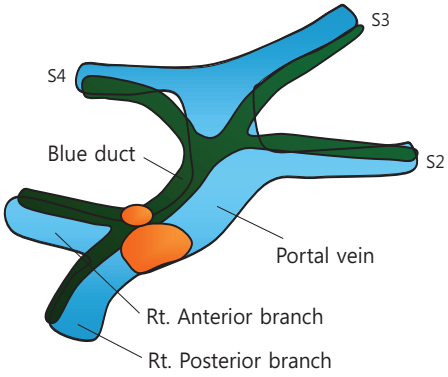


Slice thickness artifact

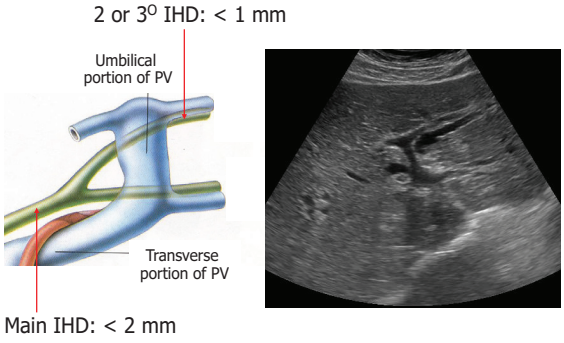


담도 초음파 스캔

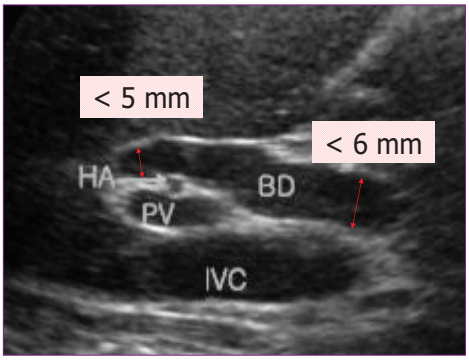
Portal vein and intrahepatic bile duct



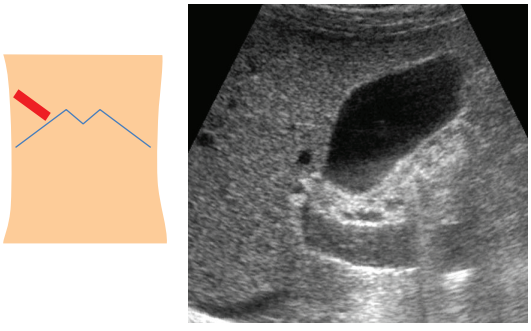
Normal anatomy of IHD



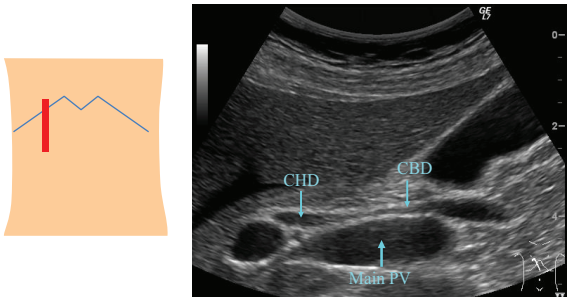
Normal Anatomy of EHD



Rt. intercostal scan

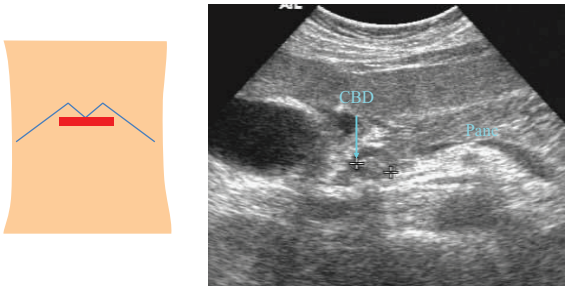


Rt. longitudinal scan



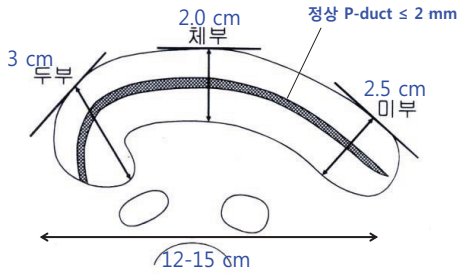
*Lt. decubitus position을 하면 distal CBD 까지 관찰 가능

Transverse scan

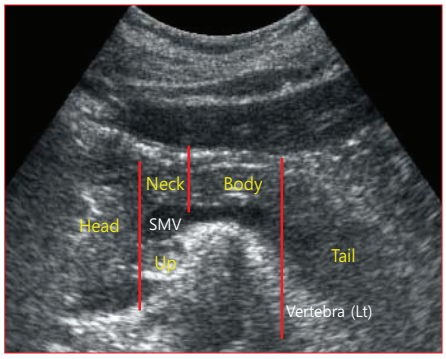


췌장 초음파 스캔

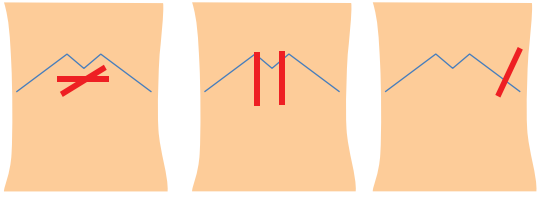
Normal ultrasonic anatomy



Ultrasonic Anatomy of the Pancreas

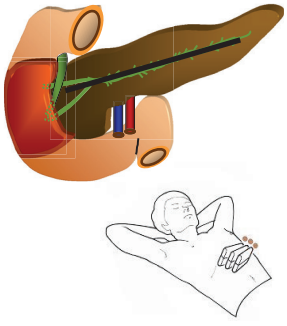


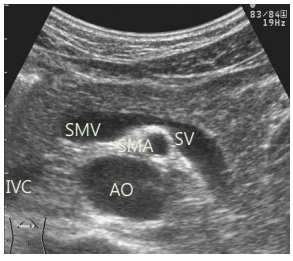
Scanning methods of the pancreas



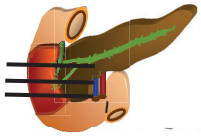
Transverse or Oblique | Longitudinal | Lt intercostal trans-splenic

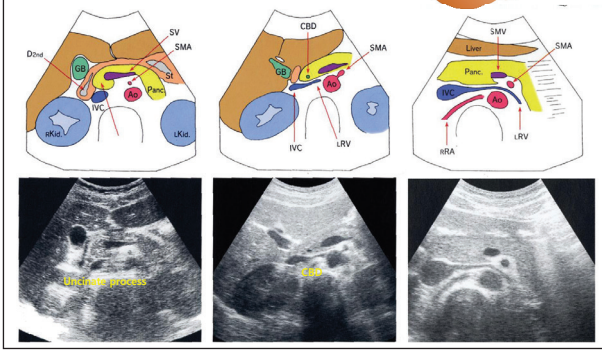
Transverse scanning



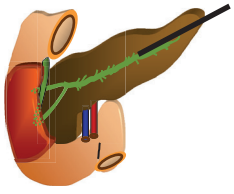


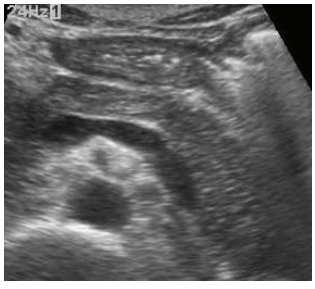
Transverse scanning



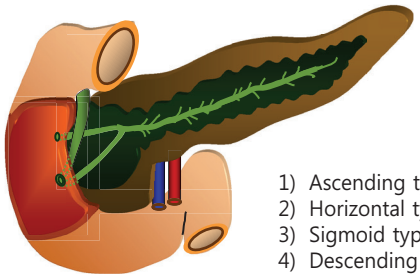


Oblique scanning



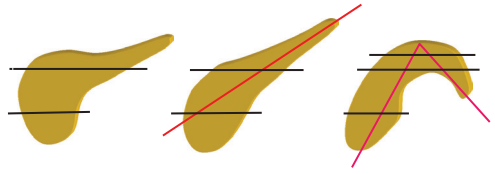


췌관의 주행

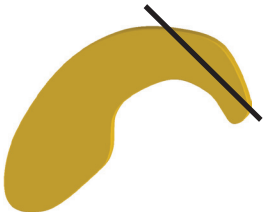


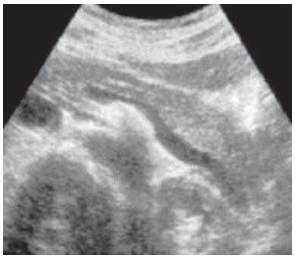
1) Ascending type
2) Horizontal type
3) Sigmoid type
4) Descending type

Transverse or Oblique Scanning

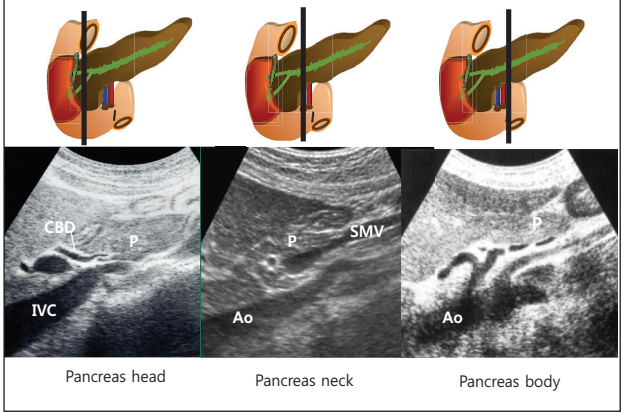


Rt. oblique scan in descending type



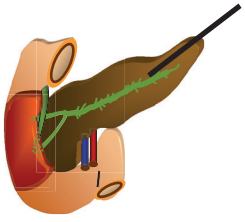


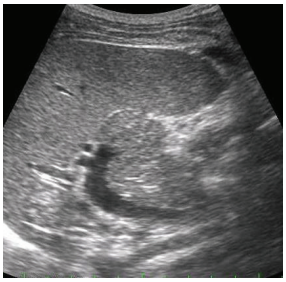
Longitudinal scan



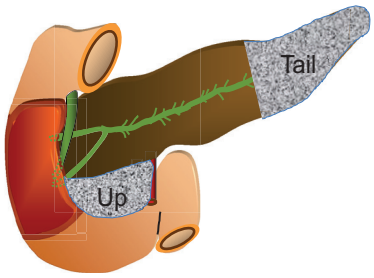
Pancreas head Pancreas neck Pancreas body

Trans-splenic view





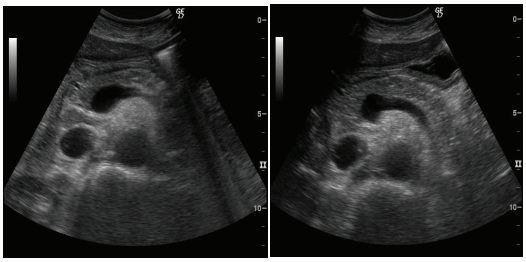
Areas of the pancreas prone to miss



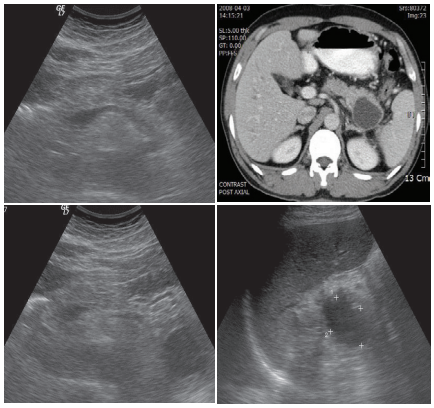
Disturbing factors for pancreas scan

- 췌장은 위, 십이지장, 장내 가스 영향으로 관찰이 어려움
  - Mechanical compression
  - Acoustic window (liver, spleen)
  - Position change (sitting position)
  - Fluid filled stomach
- 오인하기 쉬운 구조물
  - 2nd portion of duodenum → hyperechoic mass
  - Splenic artery or CHA → dilated pancreatic duct
  - Posterior wall of stomach → dilated pancreatic duct

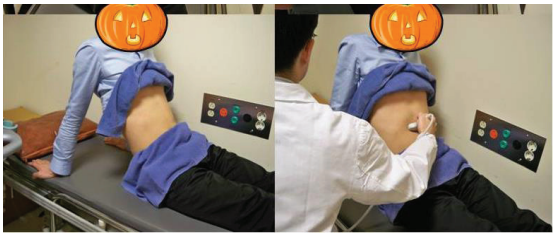
Water filling Method

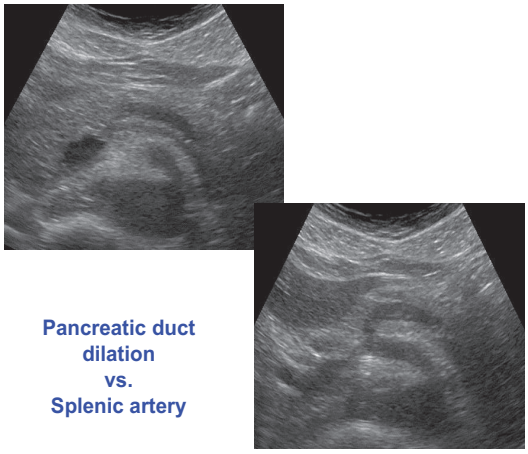


Trans-splenic view



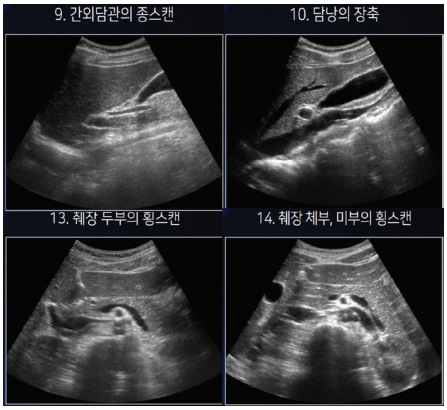
Sitting position





Pancreatic duct dilation vs. Splenic artery

췌담도 표준 영상



췌담도의 초음파검사

- ✓ 초음파의 기본 원리를 숙지
- ✓ 충분한 시간동안 세밀하게 다양한 스캔법으로 검사
- ✓ 환자의 자세를 바꾸어 검사
- ✓ 다른 영상소견 및 Clinical finding과 연동하여 검토
- ✓ 의심시에는 반복검사 및 추적검사
- ✓ 필요시에는 추가 검사; CT, ERCP, MRCP

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

DAY 2: June 21, 2019, 10:10-11:10

Plenary Session 1

Chairs : **Joung Il Lee** (Kyung Hee Univ.)
Hee Jung Wang (Ajou Univ.)
Jung-Hwan Yoon (Seoul National Univ.)

PS 1-1

The Discontinuation of Nucleos(t)ide Analogue Treatment Is Not Associated with Higher Risk of HBsAg-Seroreversion after Antiviral-Induced HBsAg-Seroclearance: A Multicenter Cohort Study

Minseok Albert Kim[1], Jeong-Hoon Lee[1], Young-Suk Lim[2], Dong Hyun Sinn[3], Yewan Park[3], Seung Up Kim[4], Sang Gyune Kim[5], Yang Hyun Baek[6], Jae-Jun Shim[7], Heejoon Jang[1], Sun Woong Kim[1], Cheol-Hyung Lee[1], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [3]Division of Gastroenterology and Hepatology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [5]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea; [6]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea; [7]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea.

Aims: The discontinuation of nucleos(t)ide analogues (NAs) is recommended when HBsAg-seroclearance is achieved during NA treatment in patients with chronic hepatitis B, although the level of evidence is not high. We aimed to evaluate whether the discontinuation of NA treatment was as safe as continuation after NA-induced HBsAg-seroclearance.

Methods: This multicenter study included 318 patients who achieved HBsAg-seroclearance during NA treatment from 7 hospitals: 159 (53.7%) stopped NA treatment within 2 months after HBsAg-seroclearance (the NA-discontinuation group) and 137 (46.3%) continued NA treatment (the NA-continuation group). Primary endpoint was HBsAg reversion and secondary endpoints included the development of HCC.

Results: During follow-up (median=32.3 months, interquartile range=0.9–124.1 months), 27 patients (8.5%) experienced HBsAg-reappearance and 7 (2.2%) developed HCC. The discontinuation of NA treatment was not an independent risk factor of HBsAg reversion (*vs*. continuation: hazard ratio [HR]=0.66, 95% confidence interval [CI]=0.30–1.44, *P*=0.30), whereas aminotransferase level of > 40 IU/L at the time of HBsAg-seroclearance (HR=2.61, 95% CI=1.11–6.13, *P*=0.03) and previous experience of ≥2 NA treatment regimens (HR=2.38, 95% CI=1.10–5.15, *P*=0.03) were (Table 1). The cumulative probabilities of HBsAg-reappearance at years 1, 3, and 5 were 4.5%, 7.9%, and 7.9% in the NA-discontinuation group; and 8.7%, 12.8%, and 12.8% in the NA-continuation group, respectively. The NA-discontinuation was not independently associated with higher risk factor of HCC development than NA-continuation (HR=0.45, 95% CI=0.05–4.33, *P*=0.49), either. Interestingly, HBsAg-seroreversion was an independent risk factor of HCC development (HR=9.01, 95% CI=1.86–43.82, *P*<0.01) (Table 2).

Conclusions: The discontinuation of NA was not associated with higher risk of either HBsAg-reappearance or HCC development among patients achieving NA-induced HBsAg-seroclearance. HBsAg-reappearance was independently associated with higher risk of HCC development.

Table 1. Cox regression analyses for HBsAg reversion

	Univariable			Multivariable*		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age ≥ 60 yr	1.41	0.63–3.13	0.40			
Male	2.11	0.80–5.58	0.13	1.91	0.72–5.10	0.20
Cirrhosis	1.95	0.90–4.22	0.10	1.46	0.67–3.21	0.34
ALT > 40 IU/L	3.16	1.37–7.27	<0.01	2.61	1.11–6.13	0.03
Exposure to ≥ 2 NAs	2.38	1.10–5.14	0.03	2.38	1.10–5.15	0.03
NA-discontinuation	0.57	0.26–1.22	0.15	0.66	0.30–1.44	0.30

HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; NA, nucleos(t)ide analogue.

*Adjusted for age, sex, ALT >40 IU/L, and NAs≥2.

Table 2. Cox regression analyses for HCC development

	Univariable			Multivariable*		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Age ≥ 60 yr	3.81	0.85–17.05	0.08	6.03	1.15–31.55	0.03
Cirrhosis	9.65	1.16–80.21	0.04	5.23	0.47–57.90	0.18
ALT > 40 IU/L	9.90	2.21–44.3	<0.01	3.71	0.67–20.71	0.14
Exposure to ≥ 2 NAs	2.46	0.55–11.02	0.24			
HBsAg reversion	13.29	2.97–59.38	<0.01	9.01	1.86–43.82	<0.01
HBV DNA redetection	1.63	0.20–13.60	0.65			
NA-discontinuation	0.14	0.02–1.20	0.07	0.45	0.05–4.33	0.49

HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; NA, nucleos(t)ide analogue.

*Adjusted for age, cirrhosis, ALT >40 IU/L, and HBsAg reversion

Keywords: Chronic hepatitis B, HBsAg-seroclearance, Nucleos(t)ide analogue, Hepatocellular carcinoma

PS 1-2

Gender Differences in the Association of Adipose Tissue and Sarcopenia in Patients with Cirrhosis

Seong Hee Kang[1,2], Soon Koo Baik[1,2], Moon Young Kim[1,2]

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, [2]Regeneration Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju, Korea

Background and Aims: We investigated the independent prognostic significance of visceral and subcutaneous adiposity in predicting mortality in cirrhosis.

Method: The skeletal muscle (SM) and adipose tissue markers, including the visceral adipose tissue index (VATI, cm^2/m^2) and the subcutaneous adipose tissue index (SATI, cm^2/m^2) were esti-

mated on computed tomography imaging in 550 patients diagnosed with cirrhosis. The cutoff values for low subcutaneous or visceral adipose tissue were adopted if SATI or VATI were lower than the mean for men and women.

Results: Most of the patients were male (79.2%) and body composition differed according to sex, with males having a greater SM index (mean, 53.2 *vs.* 47.3) and VATI (37.7 *vs.* 35.9), whereas SATI (35.9 *vs.* 68.0) was higher in females. Gender stratified analyses revealed that a high SATI was associated with overall survival (adjusted HR [aHR] = 0.29, *P*=0.02) in females, whereas sarcopenia was associated with mortality risk (aHR = 1.46, *P*=0.04) in males. In addition, male patients with sarcopenia had lower survival rates than those without sarcopenia in the low SATI group (*P*=0.01), but no difference in survival was observed according to sarcopenia in the high SATI group (*P*=0.66). Patients with a low SATI were at a higher risk of variceal bleeding than those with a high SATI (*P*<0.001). The low SATI group showed a trend toward a higher risk of developing ascites than the high SATI group, but the difference was not significant (*P*=0.07).

Conclusion: Subcutaneous adipose tissues, but not visceral adipose tissues, appear to be associated with a reduction in mortality risk, demonstrating the prognostic importance of fat distribution in female patients with cirrhosis. Moreover, the effect of sarcopenia on survival was more pronounced in male patients with a low muscle mass.

Keywords: Cirrhosis, Sarcopenia, Adipose tissue, Gender

PS 1-3

Ephrin-A3 (EFNA3) Is a Key Player in Hypoxic Microenvironment of Hepatocellular Carcinoma

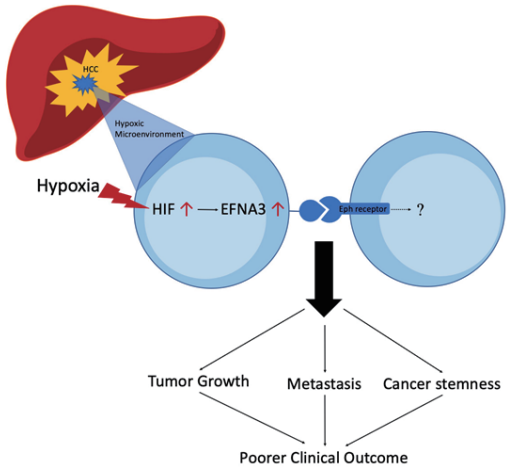
Abdullah Husain[1,2], Elley Yung-Tuen Chiu[1,2], Daniel Wai-Hung Ho[1,2], Karen Man-Fong Sze[1,2], Lo-Kong Chan[1,2], Yu-Man Tsui[1,2], Carmen Chak-Lui Wong[1,2], and Irene Oi-Lin Ng[1,2]

[1]Department of Pathology, [2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong

Aims: Intra-tumoral hypoxia is a critical driver of disease progression in hepatocellular carcinoma (HCC). However, mechanistic understanding of this phenomena is still lacking.

Methods: Integrative analysis of multiple transcriptomic profiles was performed to identify clinically relevant genes upregulated by hypoxia in HCC. EFNA3 knockdown cell models were generated to evaluate its functional role and determine the corresponding Eph receptor activity using human RTK phosphorylation antibody array. Cancer stemness marker based sorted cells from PDTX models and patients were analysed for expression of EFNA3.

Results: Our integrative analysis identified Ephrin-A3 (EFNA3) as a potential hypoxia-regulated gene target related to disease progression in HCC. EFNA3 encodes Ephrin-A3, a membrane bound ligand for multiple members of the Eph receptor family. EFNA3 was found to be significantly overexpressed in human HCC samples (n=97, p<0.0001). Clinicopathological correlation analysis revealed significant association of EFNA3 overexpression with advanced tumor stage and presence of venous invasion. Functionally, EFNA3 was upregulated in multiple HCC cell lines upon hypoxia treatment, and this upregulation was abolished upon knockdown of HIF-1α or HIF-2α. Knockdown of EFNA3 significantly reduced proliferative, migratory and self-renewal ability of HCC cells in normoxia and hypoxia *in vitro*, and resulted in lower tumor incidence rate, smaller primary tumor size and fewer lung metastases *in vivo*. HCC PDTX model sorted for multiple liver cancer stemness markers population demonstrated higher EFNA3 expression. Human HCC samples enriched for CD47 showed higher expression of EFNA3 (n=15). Moreover, EFNA3 knockdown reduced expression of CD47. Mechanistically, evaluation of relative phosphorylation levels of Eph receptors upon EFNA3 knockdown in various HCC cell lines revealed consistent inactivation of multiple candidate Eph receptors, hinting at their critical role in HCC.



Conclusions: EFNA3 was identified as a frequently overexpressed hypoxia-inducible gene in human HCC. Our findings suggests it may play a critical role in hypoxia driven disease progression of HCC.

Keywords: Hepatocellular Carcinoma, Hypoxia, Cancer stemness, Ephrin

PS 1-4

Individualized Optimization of Posttransplant Hepatitis B Prophylaxis with Hepatitis B Immunoglobulin Using Half-Life Simulation

Shin Hwang, Gi-Won Song, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tae-Yong Ha, Dong-Hwan Jung, Gil-Chun Park, Yong-Gyu Chung, Hwui-Dong Cho, Jae-Hyun Kwon, Sung-Gyu Lee

Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: Prophylaxis for hepatitis B virus (HBV) recurrence is essen-

tial after liver transplantation (LT) in HBV-associated recipients. This study established an individualized HBV prophylaxis protocol, through optimization of hepatitis B immunoglobulin (HBIG) administration, with application of simulative half-life (SHL).

Methods: This study involved five parts: Part 1 developed the SHL estimation method with 20 patients; Parts 2 and 3 assessed the SHL variability and developed a simulation model to apply SHL in 100 patients; Part 4 validated the simulation model in 114 patients, and Part 5 was a cross-sectional study on current status of HBIG infusion intervals in 660 patients.

Results: In Part 1, infusion of 10,000 IU HBIG induced add-on rise anti-HBs titer of 5252.5±873.7 IU/L, and mean SHL of 20.0±3.7 days were 4.4% lower and 2.2% longer than the actual measurements, respectively. In Part 2, the medians of the intra- and inter-individual coefficient of variation in SHL were 13.5% and 18.5%, respectively. Pretransplant HBV DNA load and posttransplant antiviral therapy did not affect SHL. In Part 3, a simulation model was developed to determine the interval of HBIG infusion, by using SHL. In Part 4, all 114 patients were successfully managed with regular HBIG infusion intervals of ≥8 weeks, and the interval was prolonged to ≥12 weeks in 89.4%, with a target trough anti-HBs titer ≥200 IU/L. In Part 5, 47.4% of our patients received HBIG excessively, at a target trough titer of 500 IU/L.

Conclusions: SHL estimation using only clinically available parameters seems to be reliably accurate when compared with actual measurements. We believe that SHL estimation is helpful to establish a personalized HBV prophylaxis protocol for optimizing HBIG administration.

Keywords: HBIG, Recurrence, Prophylaxis, Hepatitis B virus

DAY 3: June 22, 2019, 11:20-12:20

Plenary Session 2

Chairs : **Joong-Won Park** (National Cancer Center)
Han Chu Lee (Univ. of Ulsan)
Myung-Hee Yoon (Pusan National Univ.)

PS 2-1

Novel SNPs for Screening of Nonalcoholic Fatty Liver Disease: A Korean Population-Based Study

Min-Su Park

Department of Surgery, Kyung Hee University, Korea

Aims: Genetic susceptibility plays a key role in the development of nonalcoholic fatty liver disease (NAFLD). The fatty liver index (FLI) is a simple and accurate noninvasive method for predicting NAFLD. The aim of this study was to identify novel susceptibility genes associated with NAFLD as assessed by the FLI by performing a genome-wide association study (GWAS).

Methods: A prospective cohort study of 52510 adults (25840 men and 26670 women) aged 40–70 years was examined. Patients were classified into three groups by FLI (FLI <30, no NAFLD; FLI ≥60, NAFLD; and 30≤ FLI <60, intermediate FLI). To investigate the severity of fibrosis, NAFLD patients were stratified into three groups based on their NAFLD scores (NAFLD score <-1.455, low fibrosis; NAFLD score > 0.676, advanced fibrosis; and -1.455 ≤ NAFLD score ≤0.676, intermediate fibrosis). We investigated single-nucleotide polymorphisms (SNPs) related to NAFLD.

Results: After adjusting for age, sex, and body mass index, 20 SNPs in 12 genes (rs10790162, rs9326246, rs2075290, rs2266788, rs964184, rs7350481, rs780093, rs780094, rs1260326, rs10401969, rs671, rs11066280, rs11066015, rs150401869, rs1109501, rs3782886, rs76178990, rs61737409, rs201338826, and rs1448349) showed significant associations with the susceptibility to NAFLD (P<0.0001). Five genes (BUD13, GCKR, KCNQ2, MUC7, and C12orf51) of 12 genes were duplicated and meaningful. Seven SNPs in 3 genes (rs780093, rs1260326, rs1109501, rs1448349, rs780092, rs780094, and rs11249502) showed significant associations with the severity of liver fibrosis based on the NAFLD fibrosis scores.

Conclusions: We demonstrated that 20 SNPs in 12 genes are significantly associated with the presence of NAFLD in a Korean population. These findings suggest the value of genetic factors in the pathogenesis of NAFLD.

Keywords: NAFLD, Fatty liver index, GWAS

PS 2-2

Statin Use and the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

Myung Ji Goh, Dong Hyun Sinn, Wonseok Kang, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, Joon Hyeok Lee, Kwang Cheol Koh, Seung Woon Paik

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Statins have pleiotropic effects which may include chemoprevention. Several observational studies have suggested that statins may prevent hepatocellular carcinoma (HCC) but they have not yet been fully studied in patients with chronic hepatitis B virus (HBV) infections.

Methods: A hospital-based retrospective cohort of 7,713 chronic HBV-infected individuals between January 2008 and December 2012 were analyzed. The primary outcome was the development of HCC. Patients who used statins for at least 28 cumulative defined daily doses (cDDD) during the follow-up period were defined as statin users (n = 713). The association between the use of statins and the incidence of HCC was analyzed using the multivariable Cox proportional hazards model with time-dependent covariates.

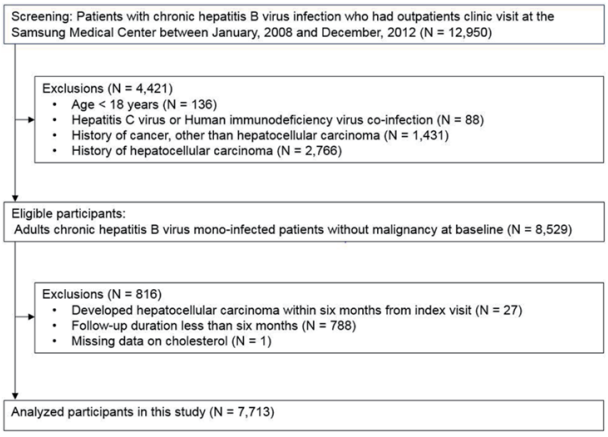


Figure 1.

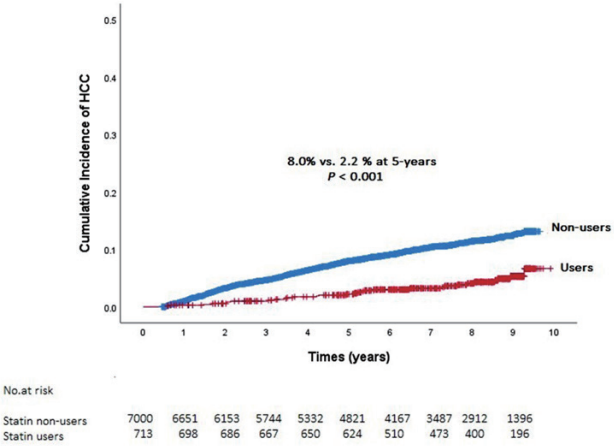


Figure 2.

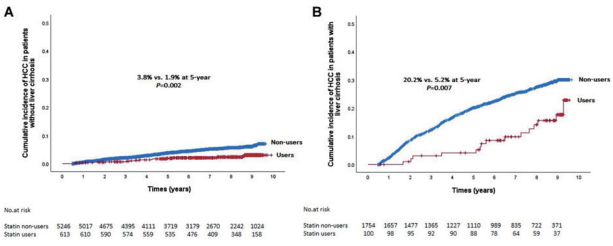


Figure 3.

Results: During a median follow-up of 7.2 years (min-max: 0.5-9.7), HCC newly-developed in 702 patients (9.1%). Statin use was associated with a lower risk of HCC (adjusted hazard ratio (HR)= 0.36, 95% confidence interval (CI): 0.19-0.68, adjusted for age, sex, cirrhosis, diabetes, hypertension, serum alanine aminotransferase, cholesterol, HBV DNA level, antiviral treatment, and antiplatelet therapy). The observed benefit of the statin was the greatest in the highest cumulative-dose group with more than 1095 cDDDs of statin (adjusted HR= 0.63, 95% CI: 0.31-1.28; HR= 0.51, 95% CI: 0.21-1.25, HR= 0.32, 95% CI: 0.07-1.35, and HR= 0.17, 95% CI: 0.06-0.48 for patients with statin use of 28-365, 366-730, 731-1095, and more than 1095 cDDDs, respectively). In subgroup analysis, the association between statin use and reduced HCC risk was significantly or marginally significantly observed regardless of status of liver cirrhosis and presence of diabetes.

Conclusions: Statin use was associated with a reduced risk of HCC development in chronic HBV-infected patients after adjustment for important confounders in a dose-dependent manner. These findings warrant a prospective evaluation.

Keywords: Statin, HCC, Liver cirrhosis, Chronic hepatitis B

PS 2-3

Robotic Major Liver Resections: Surgical Outcomes Compared with Open Major Liver Resections

Hye Yeon Yang, Seoung Yoon Rho, Dai Hoon Han, Jin Sub Choi, Gi Hong Choi

Division of Hepatobiliary and Pancreas, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

Background: Laparoscopic liver resection has been rapidly developed, laparoscopic major liver resections are still considered innovative procedures according to the second international consensus conference. Robotic surgery overcomes the limitations of laparoscopic techniques and is gaining popularity in many centers. In this study, we investigated surgical outcomes after robotic major liver resections.

Method and materials: From January 2009 to October 2018, 70 patients underwent robotic major liver resections, which included conventional major liver resections and sectionectomy of the right liver. Short-term and long-term outcomes were compared with 252 open major liver resections, which were performed during the same period.

Results: Hepatocellular carcinoma (HCC) was the most common diagnosis in robotic (n=41) and open group (n=170). Operative time was longer in robotic group (472 min vs 349 min, p<0.001), however estimated blood loss was lower in robotic group than open group (269 mL vs 548 mL, p=0.009). Postoperative complication rate of robotic group was lower than the open resection (p<0.001) Hospital stay was shorter in robotic group (9.5 days vs 15.1 days, p=0.006). There were no significant differences in overall (p=0.22,) and disease free survival (p=0.19) between the two groups in HCC. In the propensity score matching in 27 pairs with similar baseline characteristics, operative time was longer in robotic group than open group (482 min vs.374 min, p=0.04) but hospital stay was shorter in robotic group (8.9 days vs 14.4 days, p=0.001). However, there was no difference in complication rates (p=0.084) and estimated blood loss (p=0.107) between two paired group. Overall survival and disease free survival showed no difference between paired HCC groups after PSM.

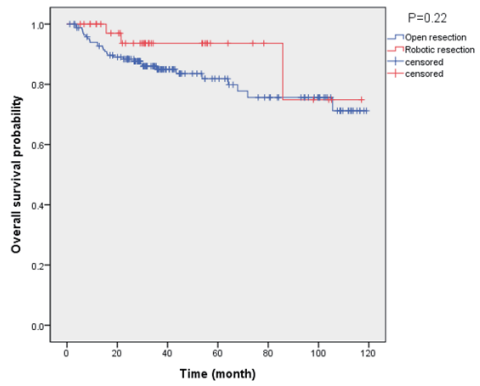
Conclusion: Robotic major liver resections showed improved perioperative outcomes and comparable long-term oncologic outcome compared with open resections. Therefore, robotic surgery should be considered one of the options for minimally invasive major liver resections.

Table 1. Patient characteristics of cohort

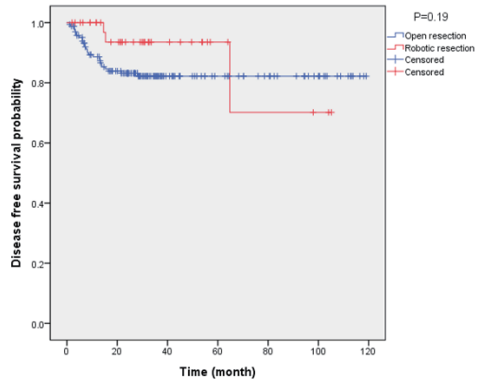
Variables (Mean ± SD)	Robotic resection (N=70)	Open resection (N=252)	p
Age (years)	53.6 ± 11.36	59.3 ± 10.1	0.797
Sex			0.044
Male	44 (62.9%)	189 (75.0%)	
Female	26 (29.2%)	63 (25.0%)	
BMI (kg/m^2)	24.1 ± 3.2	23.7 ± 3.6	0.593
Chronic liver disease			0.561
None	31 (44.3%)	104 (41.3%)	
Hepatitis B	38 (54.3%)	138 (54.8%)	
Hepatitis C	1 (1.4%)	10 (4.0%)	
Diagnosis			<0.001
Hepatocellular carcinoma	41 (58.6%)	170 (67.5%)	
Liver metastasis	8 (11.4%)	33 (13.1%)	
Intrahepatic duct stone	9 (12.9%)	2 (0.8%)	
Cholangiocarcinoma	5 (7.1%)	47 (18.7%)	
Hepatic cyst	6 (8.6%)	0 (0%)	
Cholangitis	1 (1.4%)	0 (0%)	

Table 2. Perioperative outcomes of liver resection

Variables (Mean ± SD)	Robotic resection (N=70)	Open resection (N=252)	p
Operation			<0.001
Right hemihepatectomy	17 (24.3%)	120 (47.6%)	
Left hemihepatectomy	37 (52.9%)	56 (22.2%)	
Central bisectionectomy	2 (2.9%)	26 (10.3%)	
Right posterior sectionectomy	11 (15.7%)	37 (14.7%)	
Right anterior sectionectomy	3 (4.3%)	13 (5.2%)	
Operation time (min)	472.0 ± 202.7	349.0 ± 144.7	<0.001
Estimated blood loss (ml)	269.9 ± 353.8	548.5 ± 536.7	0.009
Postoperative complication (Clavien-Dindo)			<0.001
No	48 (68.6%)	105 (41.7%)	
I, II	20 (28.6%)	126 (50%)	
III, IV	2(7.9%)	20(7.9%)	
V (death)	0(0%)	1(0.4%)	
Length of stay (days)	9.5± 6.3	15.1± 8.2	0.006

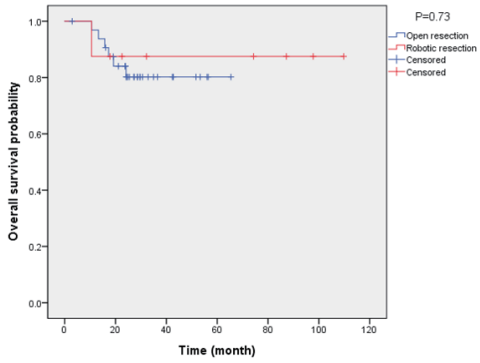


(a) Overall survival

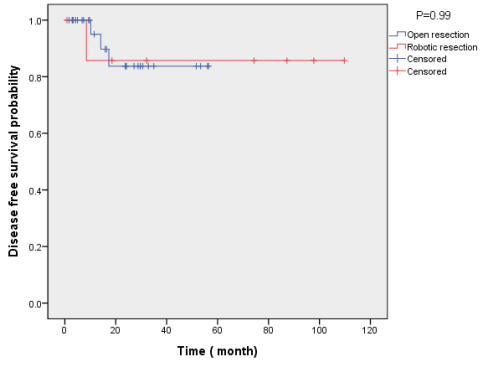


(b) Disease free survival

Figure 1. Survival analysis of hepatocellular carcinoma

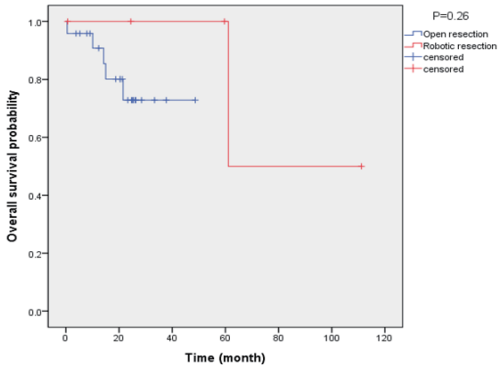


(a) Overall survival

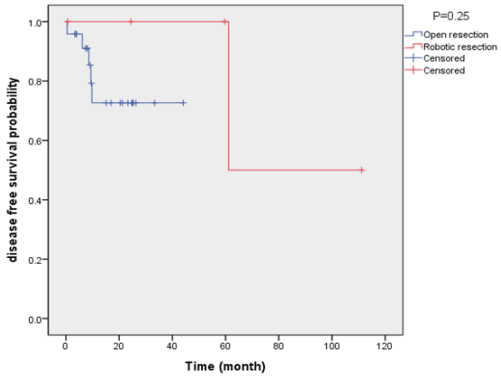


(b) Disease free survival

Figure 2. Survival analysis of liver metastasis



(a) Overall survival



(b) Disease free survival

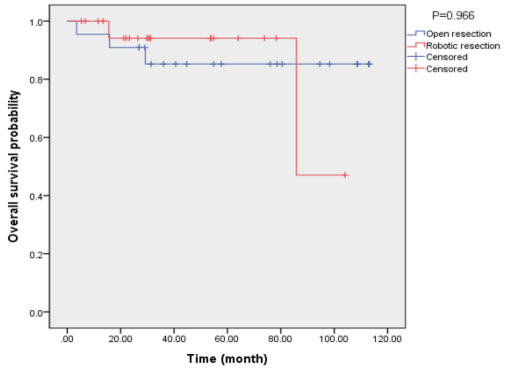
Figure 3. Survival analysis of cholangiocarcinoma

Table 3. patients characteristics between robotic anatomical resection and open resection after propensity score matching

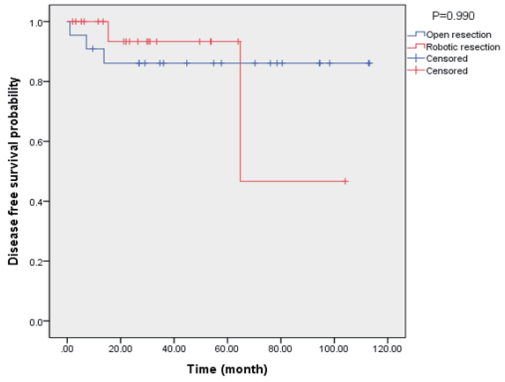
Variables (Mean ± SD)	Open resection (N=27)	Robotic resection (N=27)	p
Age (years)	56.1 ± 9.6	58.4 ± 9.1	0.377
Sex			0.499
Male	23 (85.2%)	20 (74.1%)	
Female	4 (14.8%)	7 (25.9%)	
BMI (kg/m^2)	22.9 ± 4.8	23.9 ± 2.7	0.348
Chronic liver disease			0.736
None	7 (25.9%)	9 (33.3%)	
Hepatitis B	18 (66.7%)	17 (63.0%)	
Hepatitis C	2 (7.4%)	1 (3.7%)	
Tumor size (cm)	3.2 ± 1.2	3.2 ± 1.6	0.850

Table 4. perioperative outcomes between robotic anatomical resection and open resection after propensity score matching

Variables (Mean ± SD)	Open resection (N=27)	Robotic resection (N=27)	p
Operation			0.019
Right hemihepatectomy	15 (55.6%)	9 (33.3%)	
Left hemihepatectomy	4 (14.8%)	13 (48.1%)	
Central bisectionectomy	4 (14.8%)	0 (0.0%)	
Right posterior sectionectomy	3 (11.1%)	5 (18.5%)	
Right anterior sectionectomy	1 (3.7%)	0 (0.0%)	
Length of stay	14.4 ± 6.9	8.9 ± 3.1	0.001
Operation time (min)	374.4 ± 165.8	482.3 ± 215.1	0.044
Estimated blood loss (ml)	511.5 ± 423.9	336.1 ± 359.9	0.107
Postoperative complication (Clavien-Dindo)			0.084
- No	9 (33.3%)	17 (63.0%)	
- I,II	15 (55.6%)	9 (33.3%)	
- III, IV	3 (11.1%)	1 (3.7%)	



(a) Overall survival



(b) Disease free survival

Figure 4. Survival analysis of HCC after propensity score matching

PS 2-4

Early Reduction of Regulatory T Cells by Calcineurin Inhibitor Is Associated with Acute Rejection in Liver Transplantation

Ji Won Han[1,#], Dong Jin Joo[2,#], Jong Hoon Kim[1,3], Min-Seok Rha[1], June Young Koh[1], Hye Jung Park[4], Jae Geun Lee[2], Myoung Soo Kim[2], Soon Il Kim[2], Eui-Cheol Shin[1], Jun Yong Park[4,*], Su-Hyung Park[1,*]

[1]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea; [2]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Department of Dermatology, Cutaneous Biology Research Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Department of Internal Medicine, Yonsei University College of Medicine, Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea; [#]These authors contributed equally to this work.

Aims: Regulatory T (Treg) cells are important in preventing acute rejection in solid organ transplantation, but the clinical relevance of the different kinetics after liver transplantation (LT) in acute rejectors and non-rejectors is unclear.

Methods: We analyzed peripheral blood samples of LT recipient receiving tacrolimus-based immunosuppression from a discovery cohort from 2013 to 2016 (n=64) and a validation cohort from 2017 to 2018 (n=64). Samples were obtained at pre-transplantation, D7, and D30 after LT. Treg frequency was analyzed by flow cytometry. MLR assay was performed using recipient PBMCs (pre-transplantation) and matched irradiated donor PBMCs. Apoptosis and IL-2 signaling by Tregs from recipients were investigated. The predictive value of Treg frequency at D7 was assessed in the discovery cohort and was validated in the validation cohort.

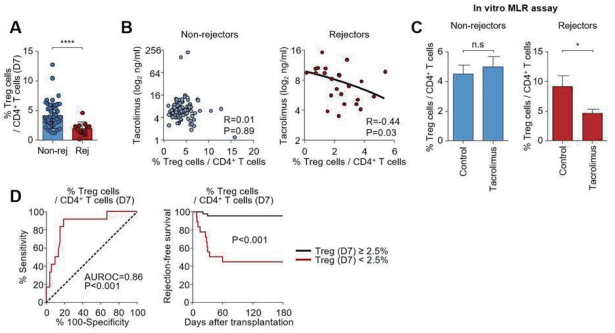


Figure 1.

Results: We found that the frequencies of total and activated Tregs at D7 were significantly lower in recipients with acute rejectors (n=12) than non-rejectors (n=52). Tacrolimus-induced Treg suppression was predominant in rejectors. Moreover, an early reduction of Treg frequency in rejectors was associated with a greater increase in Treg apoptosis and further attenuated IL-2 signaling. In multivariate analysis, Treg frequency at D7 was an independent risk factor of acute rejection (AR) and significantly predicted AR, which was subsequently validated in the validation cohort (n=64).

Conclusions: Our results suggest that first-week blood Treg frequency after LT may be a useful biomarker for predicting AR in transplant recipients under conventional immunosuppression, which may contribute to improving long-term outcomes of LT by pre-identifying recipients at risk for AR.

Keywords: Liver transplantation, Acute rejection, Regulatory T cell, Calcineurin inhibitor

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

Free Paper Session

1. HBV

June 21, 2019

O-001

Regular Follow-Up and Mortality in Patients with Chronic Hepatitis B: A National Health Insurance Cohort Study

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Aims: Chronic hepatitis B (CHB) is a major cause of liver-related mortality in Asian countries. Regular medical follow-up can be highly necessary for patients with CHB as it can increase the likelihood of treatment and surveillance testing and ultimately reduce liver-related mortality. In this large cohort study, we aimed to investigate whether regular follow-up can reduce overall or liver-cancer mortality in patients with CHB.

Methods: CHB patients who were newly diagnosed between 2007 and 2013 were collected from customized health data of Nation Health Insurance Service in Korea. The patients who developed liver cancer or died from any diseases within 2 years were excluded. Follow-up was defined when the patients were cared in clinics or hospitals under diagnosis of CHB (B180 or B181). The number of follow-up for CHB was counted every 3-month interval during 2 years after the first diagnosis. The number 0, 1 to 3, and 4 to 8 were classified as none, irregular, and regular follow-up group, respectively. Liver cancer incidence and its mortality after 2 years of diagnosis was investigated among groups.

Results: Of 414,074 patients with CHB, regular follow-up rate was 22.9%. Cirrhotic patients had more regular follow-up than non-cirrhotic patients (60.9% vs. 20.3%, P<0.0001). Although more liver cancers were diagnosed in regular follow-up group than in none follow-up group (Hazard ratio [HR], 1.538; 95% confidence interval [95% CI], 1.436–1.647; P<0.0001), liver-cancer mortality was significantly lower in regular follow-up group than in none follow-up group (HR, 0.561; 95% CI, 0.500–0.631; P<0.0001). Regular follow-up was also associated with reduced risk for overall mortality (HR, 0.597; 95% CI, 0.569–0.625; P<0.0001). The favorable effects of regular follow-up was consistently observed in both cirrhotic and non-cirrhotic patients. The best follow-up number associated with the lowest overall mortality was eight (follow-up every 3 months). Female, age > 60 years, low income, disabled state, living in rural area, and higher comorbidity rate were associated inadequate follow-up.

Conclusions: Regular follow-up at least twice a year can significantly reduce liver-cancer and overall mortality in patients with CHB.

Keywords: Hepatitis B, Chronic, Mortality, Office visits, Liver neoplasms

O-002

Bone and Renal Safety Improvements in CHB Patients Switched to Tenofovir Alafenamide (TAF) after Tenofovir Disoproxil Fumarate (TDF) Treatment

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Aims: As part of a protocol amendment to extend double blind (DB) treatment for 1 additional year (96w to 144w), only ~50% consented in time for this change; the remainder had already been receiving open-label (OL) TAF after 96w. Here, we evaluate the 4 years (192w) safety and efficacy of switching to OL TAF in patients who had received DB TDF treatment for either 2 or 3 years.

Methods: In 2 identically-designed studies, 1298 HBeAg-negative and HBeAg-positive CHB patients (873 TAF, 425 TDF) were randomized and treated with either TAF or TDF. In the TDF group, 180 patients were switched to OL TAF at 96w, while 202 patients switched at 144w. Viral suppression, biochemical responses and safety improvements were assessed at 192w using the time of rollover to TAF as the respective OL baseline(BL). Within group changes in bone and renal parameters were assessed by paired t test or Wilcoxon signed rank test.

Results: Patient characteristics were similar for those receiving OL TAF for 1 or 2 years following DB TDF treatment. Significant increases in $eGFR_{CG}$ from OL BL were observed within each group at Week 192 (Table). Significant increases in hip and spine BMD from OL BL occurred within each group. Within each group, virologic suppression (HBV DNA <29 IU/mL) was maintained from OL BL to 192w in patients who remained on TAF treatment (OL TAF 96w group: 88% and 88%; OL TAF 48w

group: 94% and 93%, respectively), while at 192w, within each group the rate of ALT normalization by 2018 AASLD criteria increased from OL BL (37%) after switching to TAF (55%).

Table 1. Renal and bone safety at year 4 (week 192)

	OL TAF 96 Wk. (N=180)	OL TAF 48 Wk. (N=202)
$eGFR_{CG}$, median (Q1, Q3) change (mL/min)	+3.0 (-2.4, +10.2) p<0.0001[a]	+1.5 (-4.8, +9.6) p=0.0212[a]
Hip BMD, mean (SD) % change	n=134 +1.25% (2.69%) p<0.0001[b]	n=190 +0.83% (2.39%) p<0.0001[b]
>3% increase / >3% decrease in hip BMD	18.7% / 5.2%	11.6% / 2.6%
Spine BMD, mean (SD) % change	n=133 +1.56% (3.39%) p<0.0001[b]	n=190 +1.62% (3.12%) p<0.0001[b]
>3% increase / >3% decrease in spine BMD, (%)	34.6% / 9.0%	27.9% / 5.8%

All results expressed as change from open-label (OL) baseline (defined as Week 96 for OL TAF 96 Wk and Week 144 for OL TAF 48 Wk patients). $eGFR_{CG}$ is creatinine clearance by Cockcroft-Gault method, BMD is bone mineral density by dual energy x-ray absorptiometry (DXA), Q is quartile. [a]Week 192 vs OL baseline by Wilcoxon signed rank test; [b]Week 192 vs OL baseline by paired t test.

Conclusions: In CHB patients treated with TDF for 2 or 3years, recovery of renal and bone parameters occurred at 4y suggesting reversibility of these parameters. Virologic control was maintained and ALT normalization increased following the switch from TDF to TAF.

Keywords: HBV, TAF, BMD, Renal improvement

O-003

A Phase 3, Stable Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF) in Chronic Hepatitis B (CHB) Patients: 48w Results

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Background and Aims: TAF, a novel prodrug of tenofovir (TFV), has greater plasma stability and reduced circulating levels of TFV compared to TDF at approved doses. TAF has shown efficacy non-inferior to TDF with improved renal and bone safety in viremic CHB patients. We evaluated efficacy and safety in stable, virally-suppressed patients who were switched from TDF to TAF vs. continued TDF for an additional year.

Methods: In this Phase 3 study (NCT02979613), CHB patients on TDF for ≥48w with HBV DNA <LLOQ (local laboratory) for ≥12w and <20 IU/mL at screening were randomized (1:1) to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo, and treated for 48w. After this, all patients received open-label TAF for an additional 48w. The primary efficacy analysis was the proportion of patients with HBV DNA ≥20 IU/mL at 48w based on the modified US FDA-defined Snapshot algorithm. Key prespecified secondary safety endpoints were changes in hip and spine bone mineral density (BMD), and changes in $eGFR_{CG}$.

Results: 488 patients were randomized and treated at 42 sites in 8 countries. At baseline the groups were similar: median age 52y (22% ≥60y), 71% male, 82% Asian, 68% HBeAg-negative, and median ALT 23 U/L. Median $eGFR_{CG}$ was 90.5 mL/min; 45% and 50% had low BMD by T scores at hip and spine, respectively. Median (Q1, Q3) duration of prior TDF was 222 (145, 305) weeks. Key efficacy/safety results are summarized in the Table. TAF demonstrated non-inferior efficacy to TDF and TAF treatment resulted in increases in hip/spine BMD with less impact on bone turnover makers; switching from TDF to TAF also resulted in increased $eGFR_{CG}$ and decreases in markers of tubular function.

Table

n/N (%)	TAF (N=243)	TDF (N=245)	P value
Efficacy			
HBV DNA ≥20 IU/mL[a]	1/243 (0.4)	1/245 (0.4)	0.95[b]
HBV DNA <20 IU/mL	234/243 (96.3)	236/245 (96.3)	0.98
No virologic data in Week 48 window	8/243 (3.3)	8/245 (3.3)	-
ALT normal (2018 AASLD criteria)[c,d]	192/243 (79)	184/245 (75.1)	0.31
HBeAg seroconversion[e]	2/78 (2.6)	0	0.13
HBsAg seroconversion	0	0	-
Bone safety			
Hip BMD, mean (SD) % change	+0.66 (2.08)	-0.51 (1.91)	<0.001
Spine BMD, mean (SD) % change	+1.74 (3.46)	-0.11 (3.13)	<0.001
CTX, median (Q1, Q3) % change (ng/mL)[f]	-29.4 (-44.2, -14.3)	+7.1 (-14.8, 32)	<0.001
P1NP, median (Q1, Q3) % change (ng/mL)[g]	-19.4 (-32.2, -7.5)	+1.70 (-12.5, 17)	<0.001
Renal safety			
$eGFR_{CG}$, median (Q1, Q3) change (mL/min)	+0.99 (-4.47, 6.31)	-2.74 (-7.87, 1.98)	<0.001
RBP/Cr, median (Q1, Q3) % change[h]	-17.7 (-41.3, 17.2)	+18.6 (-15.3, 67.3)	<0.001
β2MG/Cr, median (Q1, Q3) % change[i]	-36.0 (-61.9, -1.1)	+10.7 (-33.9, 90.6)	<0.001

[a]HBV DNA results by modified US FDA Snapshot algorithm; other efficacy data are missing=failure. [b]Stratified Cochran-Mantel-Haenszel test. [c]ALT normal is the proportion with ALT ≤ULN at Week 48, regardless of baseline status. [d]ULN 35 U/L males, 25 U/L females; [e]HBeAg-positive at baseline. [f]C-type collagen sequence (bone resorption marker); [g]Procollagen type 1 N-terminal propeptide (bone formation marker); [h]Retinol binding protein/creatinine (tubular marker); [i]Beta-2 microglobulin/creatinine (tubular marker).

Conclusion: Virologically-suppressed CHB patients who were switched to TAF demonstrated noninferior efficacy to continued TDF with improved bone and renal safety.
Keywords: TAF, Stable switch, TDF, Swtich

O-004

Tenofovir Disoproxil Fumarate Directly Regresses Liver Fibrosis by Inducing Hepatic Stellate Cell Apoptosis

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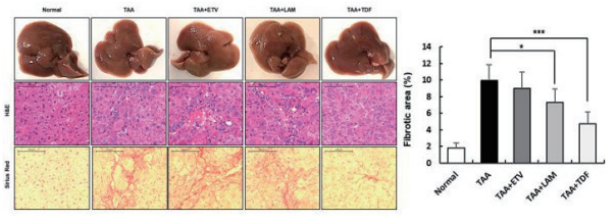
Aims: The treatment with tenofovir disoproxil fumarate (TDF) results in the regression of liver fibrosis but its underlying mechanism has not been clarified thus far. We aimed to evaluate the direct association between TDF treatment and the activated hepatic stellate cells (HSCs) which are major sources of fibrogenic liver cells.
Methods: - *In vitro* experiment; Activated hepatic stellate cell lines, LX2 and HSC-T6 were used to evaluate the effect of antiviral agents entecavir (ETV), lamivudine (LAM) and TDF on HSCs. After treatment with each antiviral agent, cell viabilities were detected using the MTT assay, apoptotic features were quantified by Annexin V assay and the apoptosis signaling pathways were determined by western blot. Apoptotic nuclei were visualized using Tunel staining.
- *In vivo* experiment; In mouse liver fibrosis models induced by thioacetamide (TAA), ETV, LAM and TDF were given by oral gavage every day for 10 weeks. After sacrificing the mouse, the collagen deposition in the liver was assessed by Sirius red staining and quantified. a-SMA and TIMP-1, serum ALT and creatinine were measured. Apoptotic nuclei were visualized using Tunel staining.
Results: The cell viabilities of LX2 and HSC-T6 cells decreased after TDF treatment but not after ETV or LAM. TDF-treated cells showed morphological changes compatible with apoptosis. Annexin-V assay demonstrated that TDF-induced HSC death was due to apoptosis and after Tunel staining, TDF-treated HSCs showed increased apoptotic features. Regarding the apoptosis signaling pathways, PARP and Caspase-3 were cleaved with inhibition of the anti-apoptotic gene, Bcl-xl following TDF treatment.
In TAA-induced liver fibrosis mouse model, significantly decreased fibrotic areas were observed in the TDF group compared to ETV and LAM. Also, a-SMA and TIMP-1 were significantly decreased in the TDF group. Tunel staining demonstrated that the apoptotic nuclei were concentrated surrounding the portal vein tract merging on a-SMA stains which indicated the apoptosis of HSCs. In terms of toxicity, serum ALT and creatinine were not significantly elevated after TDF.
Conclusions: Our experiment has demonstrated, for the first time, that TDF directly regresses liver fibrosis by inducing HSC apoptosis. Anti-fibrotic effects of TDF may be taken into account as a factor in the selection of antiviral drug for CHB patients and TDF may be considered as a therapeutic agent for the treatment of liver fibrosis.

Decreased collagen deposition and fibrotic area were observed after TDF compared to ETV and LAM



Keywords: Tenofovir, Stellate cell, Apoptosis, Liver fibrosis

O-005

Risk of Hepatocellular Carcinoma in Patients with Immune-Tolerant Chronic Hepatitis B

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Aims: Recent studies have suggested that patients with immune-tolerant chronic hepatitis B (CHB), characterized by hepatitis b e antigen (HBeAg) positive patients with high serum hepatitis B virus (HBV) DNA but normal alanine aminotransferase (ALT), may develop hepatocellular carcinoma (HCC). However, it is unclear how to stratify HCC risk in these patients.
Methods: A retrospective cohort of 651 HBeAg positive, adult patients with high serum HBV DNA levels (>7 log IU/mL) but normal or mildly elevated ALT levels (<80 U/L) were analyzed. Age and FIB-4 index were used to categorize patients, and assessed actual HCC incidence rate in each subgroups. Normal ALT was defined as <35 U/L for males and <25 U/L for females.
Results: During a median 5.2 years of follow-up (range: 1.0-17.8 years), 24 (3.7%) patients developed HCC. Age and FIB-4 index were independent factors associated with HCC development. When stratified, 5 and 10-year cumulative HCC incidence rates were 0% and 2.0% for patients aged <40 years plus FIB-4 index <1.45, and were 5.9% and 32.7% for patients aged ≥40 years plus FIB-4 index ≥1.45, respectively (P<0.001). When analysis was limited to patients with normal ALT levels (n = 301), 10-year HCC incidence rate was 0% for patients aged <40 years plus FIB-4 index <1.45, while 5 and 10-years HCC incidence rate was 4.5% and 27.1% for patients aged ≥40 years plus FIB-4 index ≥1.45, respectively (P<0.001).
Conclusions: In patients with immune-tolerant CHB, HCC risk was considerably high for aged patients with elevated FIB-4 index while HCC risk was very low for young patients with low FIB-4 index. These two factors could effectively stratify HCC risk, indicating that they may guide management plan for this

population.

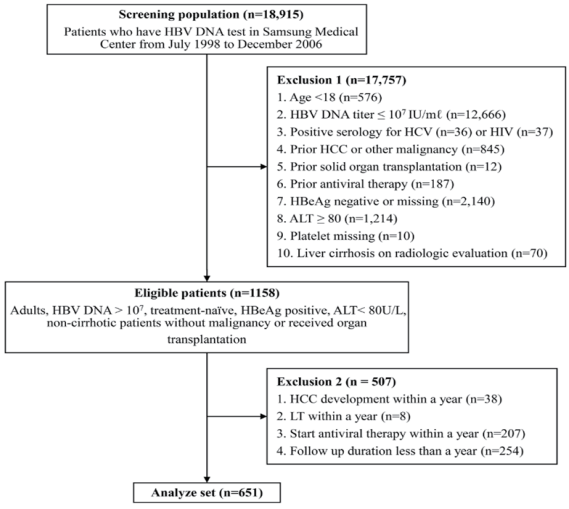

Figure 1.

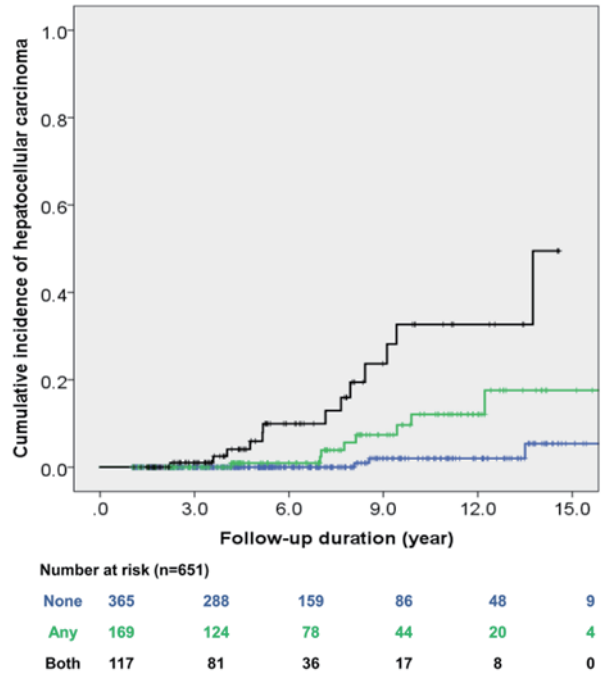

Figure 2.

Keywords: Hepatitis B virus infection, Age, Fibrosis-4, Antiviral treatment

O-006

Detection of HBV Integration in the Human Genome Using High-Throughput Targeted Sequencing

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Aims: While it has long been known that hepatitis B virus (HBV) integrates into the host genome, the biological role of the integrated HBV DNA in hepatocarcinogenesis still remains uncertain. The study aimed to localize HBV integrants throughout the host genome by high-throughput sequencing method.

Methods: Next-generation sequencing (NGS)-based target enrichment sequencing was performed to detect HBV integration in paired tumor/non-tumor tissues from 33 hepatocellular carcinoma (HCC) patients. The Illumina NGS workflow was conducted in the following steps: gDNA sonication to generate DNA libraries, HBV sequence capture using HBV probes, followed by high-throughput sequencing. Chimeric Count >10 and AVG_MQ >20 was regarded as true signal. Sanger sequencing was done to verify the HBV-integrated breakpoints.

Results: HBV integration was identified in all (25/25, 100%) HBsAg-positive and 2 (2/8, 25%) HBsAg-negative patients with HCC. Two patients who lost HBsAg before HCC development also harbored HBV integration in both tumor and non-tumor tissues. The average number of integration sites in HBV-related HCC and adjacent non-tumor tissues was 12.45 and 24.04 per sample, respectively. HBV integration most frequently occurred in chromosomes 5 and 10. Recurrent target genes for HBV integration included TERT, MLL4, and PREX2 for tumor and FN1 for non-tumor. The major hotspot breakpoints of host and HBV genomes were located at upstream of hTERT gene and nt 1600-1800 of HBV genome, respectively. Integrations in tumor were over-presented in promoter or exon and less presented in intergenic region. Gene-annotation analysis indicated that the recurrent HBV integrations are enriched in cancer-associated genes. HBV integration breakpoints were validated by Sanger sequencing in six randomly selected tumor tissues.

Conclusions: Our study reports a new high-throughput targeted sequencing using NGS method with high detection ability to identify HBV integration in the human genome. This cost-effective method facilitates a survey of HBV integration in a large number of samples in an unbiased way.

Keywords: Hepatitis B virus, Integration, Carcinogenesis, Sequencing

2. ALD & NAFLD

O-007

Incidence and Risk Factors Analysis of Liver Cancer in Patients with Alcoholic Liver Disease: Retrospective Cohort Analysis of 5,160 Patients

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Aims: Alcohol increases the risk of liver cancer, but the incidence and predictor of liver cancer have not been well defined in alcoholic liver disease (ALD). This retrospective cohort study aimed to investigate the incidence and risk factors of liver cancer development in the patients with ALD on surveillance.

Methods: A total of 5,160 patients were diagnosed as ALD and followed for more than 6months from Apr 2004 to Dec 2017 in our single center. ALD cases were identified by the ICD10 of K70. Surveillance for liver cancer was based on liver ultrasound and / or serum tumor marker such as alpha fetoprotein (AFP) and carbohydrate antigen 19-9 (CA 19-9). Liver cancer incidence and related risk factors were analyzed by Kaplan-Meier analysis and competing risk Cox model.

Results: During a median follow-up of 5.4 years, a total of 153 patients were newly diagnosed as liver cancer including 146 cases of HCC, 6 cases of Intrahepatic cholangiocarcinoma and 1 case of combined HCC-CCC, retrospectively. Overall liver cancer incidence was 0.9% at 2 years, 2.9% at 5 years, 5.2% at 10 years and 8.7% at 15 years. In patients with liver cirrhosis, liver cancer incidence was 3.8% at 2 years, 13.3% at 5 years, 24.1% at 10 years, and 33.5% at 15 years. Cox multivariate analysis showed that the independent factors related to liver cancer development were male sex (hazard ratio [HR], 2.84; 95% confidence interval [CI], 1.60-5.04; P<0.01), old age (HR, 1.05; 95% CI, 1.03-1.06; P<0.01), cirrhosis (HR, 22.69; 95% CI, 12.63-40.78; P<0.01), low serum platelet count (≤110,000/uL; HR, 1.83; 95% CI, 1.24-2.71, P=0.002), positive serum Hepatitis B surface antigen (HBsAg) (HR, 3.10; 95% CI, 2.07-4.64; P<0.01), and positive serum anti-HCV antibody (HR, 2.07; 95% CI, 1.18-3.66; P=0.012).

Conclusions: Liver cancer incidence among alcoholic liver disease was 0.9%, 2.9%, 5.2%, 8.7% at 2, 5, 10, 15 years, respectively. Male sex, old age, cirrhosis, serum platelet count, positive serum HBsAg, and positive Anti-HCV antibody were independent risk factor for liver cancer development in patients with ALD.

Keywords: Alcoholic liver disease, Liver cancer, Surveillance, Incidence, Risk factors

O-008

Algorithms Using Noninvasive Tests Can Accurately Identify Patients with Advanced Fibrosis Due to NASH: Data from the STELLAR Clinical Trials

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Aims: There is a major unmet need for accurate, readily available, noninvasive tests (NITs) to identify patients with advanced fibrosis (F3-F4) due to NASH. Our goal was to evaluate sequential NIT algorithms to minimize the requirement for biopsy and improve accuracy over use of single tests.

Methods: The STELLAR studies (NCT03053050, NCT03053063) enrolled NASH patients with bridging fibrosis (F3) or compensated cirrhosis (F4). Baseline liver biopsies were centrally read using the NASH CRN fibrosis classification and noninvasive fibrosis markers, including the Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) test, and FibroScan® (FS) were measured. The performance of these tests to discriminate advanced fibrosis was evaluated using AUROCs with 5-fold cross-validation repeated 100x. Thresholds were obtained by maximizing specificity given ≥85% sensitivity (and vice versa). The cohort was divided (80%/20%) into evaluation/validation sets. The evaluation set was further stratified 250x into training and test sets (66%/33%). Optimal thresholds were derived as the average across training sets, and applied sequentially (FIB-4 followed by ELF and/or FS) to the validation set. Data are from an interim analysis on 26 July 2018.

Results: All patients with available liver histology (N=3202, 71% F3-F4) and NIT results were included. While single tests were able to discriminate advanced fibrosis (AUROCs of 0.78, 0.80, and 0.80 for FIB-4, ELF, and FS in validation cohort), up to 32% of patients had an indeterminate result. Using thresholds derived from STELLAR data, FIB-4 followed by FS or ELF in those with indeterminate FIB-4 values (1.23 to 2.1) reduced indeterminate results to as low as 13% (Table). Published NIT thresholds yielded similar results (data not shown). Adding a third test (FIB-4 then ELF then FS) reduced the rate of indeterminate results to 8%. Misclassification occurred at rates similar to biopsy (15-21%). The majority of misclassifications (63-81%) were false negatives; among false positive cases (19-27% of misclassifications), up to 70% had F2 fibrosis.

Conclusions: In these large, global, phase 3 trials with newly derived thresholds optimized for the STELLAR trials, FIB-4 followed

by ELF and/or FS nearly eliminated the need for liver biopsy and accurately identified patients with advanced fibrosis due to NASH with misclassification rates similar to liver biopsy.

Table: Diagnostic Performance of NITs to Discriminate Advanced Fibrosis (F3-F4)

Test*	Cohort	Sample Size	Sensitivity	Specificity	Indeterminate	Misclassified**
FIB-4 (1.23, 2.1)	Train+Test	2496	85%	85%	32%	15%
	Validation	627	83%	89%	32%	15%
ELF (9.35, 10.24)	Train+Test	2536	85%	85%	29%	15%
	Validation	637	85%	85%	29%	15%
FS (9.6kPa, 14.53kPa)	Train+Test	1408	85%	86%	28%	15%
	Validation	357	82%	88%	25%	17%
FIB-4 (1.23, 2.1) then ELF (9.35, 10.24)	Train+Test	2542	79%	81%	13%	20%
	Validation	638	78%	82%	13%	21%
FIB-4 (1.23, 2.1) then FS (9.6kPa, 14.53kPa)	Train+Test	2509	82%	85%	20%	17%
	Validation	632	78%	87%	20%	19%

*Lower value represents optimal threshold to exclude advanced fibrosis, higher value to diagnose advanced fibrosis, with in-between values classified as indeterminate
**Proportion of misclassified patients relative to total sample size including indeterminate zone

Keywords: NASH, NAFLD, Gilead, Selonertib, ASK-1 inhibitor, STELLAR, Fibrosis, Non-invasive test

O-009

Development of Diagnostic Marker for NASH and Evaluation of Hepatic Steatosis and Fibrosis Using Biochemical Marker, TE, and MRI in Biopsy-Proven NAFLD Patients

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Aims: Nonalcoholic fatty liver disease (NAFLD) is becoming a major cause of chronic liver disease. The development of non-invasive evaluation of severity in this broad spectrum disease is urgently needed. In this prospective cross-sectional study, we aimed to evaluate hepatic steatosis and fibrosis using non-invasive tests including biochemical marker, transient elastography (TE), and magnetic resonance imaging (MRI). In addition, we tried to develop non-invasive diagnostic marker for NASH using biochemical parameters and MRI parameters.

Methods: This is a prospective cross-sectional study including patients with biopsy-proven NAFLD. All patients underwent biochemistry, TE, and MRI within 6 months of liver biopsy. For evaluation of biochemical fibrosis marker, AST/platelet ratio index (APRI) and fibrosis-4 (FIB-4) index were calculated in all patients. MRI examination included mDIXON, MR spectroscopy (MRS), T1 mapping and MR elastography (MRE). TE measured liver stiffness and controlled attenuation parameter (CAP).

Results: 123 patients with biopsy-proven NAFLD were enrolled from October 2016 to March 2019. Mean age and BMI were 50.69 ± 13.57 years and 29.59 ± 4.64 kg/m^2, respectively. Female was dominant (n=72, 58.5%) and other co-morbidities were checked, such as diabetes (n=52, 42.3%), hypertension (n=53, 43.1%) and dyslipidemia (n=39, 31.7%). For diagnosis of severe steatosis (stage 2-3), CAP (0.706; 95% CI, 0.595-0.802) showed lower AUROC compared with mDIXON (0.832; 95% CI, 0.733-0.905; *P*=0.027) and MRS (0.842; 95% CI, 0.744-0.913; *P*=0.029), respectively (FIgure 1). For diagnosis of advanced fibrosis (stage 3-4), diagnostic accuracy of MRE was superior (0.889; 95% CI, 0.748-0.915) comparing with APRI (0.686; 95% CI, 0.623-0.725, *P*=0.003), FIB-4 (0.808; 95% CI, 0.743-0.845, *P*=0.018), and TE (0.829; 95% CI, 0.683-0.870, *P*=0.016) (Figure 2). Age, BMI, DM, dyslipidemia, AST, platelet are associated with NASH in univariate. In multivariate analysis AST, PLT, and MRE were significant factor for diagnosis of NASH.

Conclusions: MRI (mDIXON, MRS and MRE) showed significant diagnostic accuracy to identify severe steatosis and advanced fibrosis compared to other non-invasive markers in patients with biopsy-proven NAFLD. AST, PLT, and MRE were significant factor for diagnosis of NASH. Non-invasive modalities using AST, platelet, and MRI could be potential tools for diagnosis of NASH.

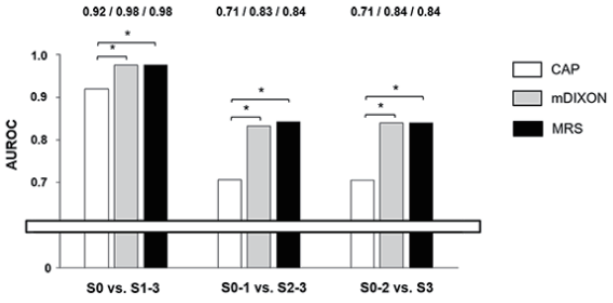

Figure 1.

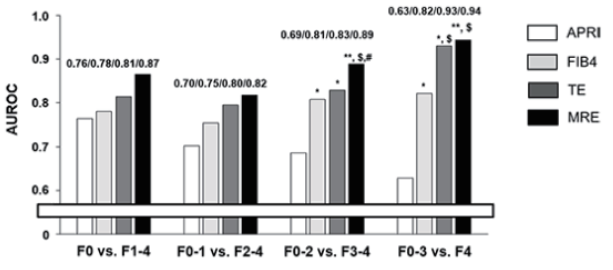

Figure 2.

Keywords: NAFLD, NASH, MRI, Elastgraphy

O-010

The Impact of Controlled Attenuation Parameter on Liver Stiffness Measurement Using Transient Elastography in Patients with Nonalcoholic Fatty Liver Disease

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Aims: According to a recent report, severe steatosis is likely to affect liver elasticity (E) as measured by transient elastography (TE) in subjects with non-alcoholic fatty liver disease (NAFLD). However, little is known about the impact of controlled attenuation parameter (CAP) as assessed by TE on the measurement of liver E in subjects with NAFLD.

Methods: Five hundred fifty-nine subjects with biopsy-proven NAFLD were included in this prospective analysis. All patients underwent TE with CAP measurement. Logistic regression analysis and discriminant function analysis were used for calculating two kinds of CAP-adjusted E. Area under ROC curves (AUROC) were used to determine the optimal cut-offs, sensitivity, and specificity of CAP-adjusted E values for detecting significant fibrosis (≥F2) and advanced fibrosis (≥F3).

Results: For diagnosing significant fibrosis, the AUROCs for TE (CAP-adjusted E) were 0.817 (optimal cut-off, -0.189; sensitivity [se], 72.68%; and specificity [sp], 79.78%) in model 1 (adjusted for CAP) and 0.812 (optimal cut-off, -0.042; se, 67.60%; sp, 82.70%) in model 2 (adjusted for CAP, platelet, albumin, and PT INR) by formula calculated using discriminant function analysis, while, for diagnosing advanced fibrosis, those for TE (CAP-adjusted E) were 0.908 (optimal cut-off, 0.274; se, 80.49%; sp, 93.43%) in model 1 and 0.916 (optimal cut-off, 0.205; se, 82.05%; sp, 89.38%) in model 2 by formula calculated using discriminant function analysis. The AUROCs (for ≥F2, 0.821 and for ≥F3, 0.914) for TE (E) were not significantly different from those for TE (CAP-adjusted E).

Conclusions: There was a significant positive correlation between CAP-adjusted E and fibrosis stages in subjects with NAFLD. However, CAP-adjusted E was not superior to E in diagnosing significant fibrosis and advanced fibrosis.

Keywords: NAFLD, LSM, CAP, Fibrosis

O-011

Serial Liver Stiffness and Controlled Attenuation Parameter Measurements by Transient Elastography in Patients with Type 2 Diabetes

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Aims: Type 2 diabetes is an important risk factor for non-alcoholic fatty liver disease (NAFLD) and advanced fibrosis. Current European guidelines recommend repeating non-invasive tests of fibrosis in NAFLD patients at 3-yearly intervals, but data are largely lacking. Here we report the changes in the liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by transient elastography (TE) in patients with type 2 diabetes at 3 years.

Methods: We recruited patients with type 2 diabetes from a complication screening facility in Hong Kong in 2013-2014 and repeated the assessment in 2016-2018. The primary endpoint was the proportion of patients who progressed to chronic liver disease with advanced fibrosis The secondary endpoint was the proportion of patients who experienced a change in the CAP.

Results: A total of 611 diabetic patients with valid LSM (mean age, 57.7 ± 10.9 years; 342 males [56.0%]) were included in this study (568 also had valid CAP). Overall, there was moderate correlation between baseline and follow-up LSM (r=0.689, *P*<0.001). At baseline, 487 (79.7%) patients had an LSM <10 kPa and 21 (4.3%) had follow-up LSM ≥10 kPa. BMI, ALT and ΔALT were independent factors for predicting LSM increase. Among the remaining 124 (20.3%) patients with LSM ≥10 kPa at baseline, 70 (56.5%) had follow-up LSM <10 kPa. Among 198/568 (34.9%) patients with CAP <248 dB/m at baseline, 103 (52.0%) had CAP increased to ≥248 dB/m (55 [27.8%] ≥280 dB/m suggestive of severe steatosis). Among the 370/568 (65.1%) patients with a CAP ≥248 dB/m at baseline, CAP decreased to <248 dB/m in 45 (12.2%) patients.

Conclusions: The prevalence and incidence of NAFLD in patients with type 2 diabetes are high. While patients with advanced fibrosis are common in this population, the incidence of progression to advanced fibrosis is relatively low. Our results support one-off fibrosis testing in diabetic patients but not routine 3-yearly assessments in all patients.

Keywords: Diabetes, NAFLD, Controlled attenuation parameter, Liver stiffness measurement

O-012

Relationship between Incident Nonalcoholic Fatty Liver Disease and Body Composition Parameters at Baseline and during Follow-Up: A 8-Year Longitudinal Study

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Republic of Korea

Aims: Association between nonalcoholic fatty liver diseases (NAFLD) and relative skeletal muscle mass has been documented in several studies. We investigated the effects of baseline values and changes of body composition and development of incident NAFLD in a large-scale longitudinal cohort study.

Methods: In this 8-year longitudinal study, we included a total of 9967 subjects without NAFLD at baseline who underwent two or more comprehensive health check-up examinations between January 2008 and December 2016. We explored association between development of incident NAFLD and body composition parameters at baseline as well as their changes, including body weight-adjusted soft lean mass and percentage fat.

Results: Study subjects were categorized according to their BMI as follows: underweight (BMI<18.5), n=710 (7.1%); lean (18.5≤BMI<23), n=5457 (54.8%); overweight (23≤BMI<25), n=2182 (21.9%); obese (BMI>25), n=1618 (n=16.2%). During follow-up, incident NAFLD was observed in 2395 subjects (24.0%). Subjects with incident NAFLD were older (47.1 vs. 45.6 years), male-predominant (55.2% vs. 32.9%), had higher baseline BMI (23.7 vs. 21.8), and were more frequently associated with MetS (53.1% vs. 33.6%), compared to those without (all *P*<0.001). Among the subgroups by BMI, incident NAFLD developed in 2.0% in the underweight group, 40.0% in the lean group, 27.6% in the overweight group, and 30.4% in the obese group, respectively (*P*<0.001). Baseline risk factors for incident NAFLD in each BMI subgroup were as follows: i) underweight group: higher serum glucose (hazard ratio [HR]=1.1; 95% confidence interval [CI], 1.02-1.08; *P*<0.001) and triglyceride level (HR=1.0; 95% CI, 1.00-1.02; *P*=0.01); ii) lean group: higher percentage fat (PF; HR=1.1; 95% CI, 1.10-1.16; *P<0.001), lowest tertile of soft lean mass/weight (SLM/Wt; HR=2.4; 95% CI, 1.9-2.9; P<0.001), No. of MetS components ≥ 2 (HR=2.3; 95% CI, 1.88-2.84; P*<0.001); iii) overweight group: higher PF (HR=1.1, 95% CI, 1.02-1.10; *P*<0.001); No. of MetS components ≥ 2 (HR=1.6; 95% CI, 1.27-1.96; *P*<0.001); iv) obese group: higher PF (HR=1.0; 95% CI, 1.00-1.05; *P*<0.001), No. of MetS components ≥ 2 (HR=1.4; 95% CI, 1.16-1.68; *P*<0.001) Of the entire study population, 5033 subjects underwent health examination three or more times during the study period, with their second examination after a median of 1.2 years (IQR, 1.0-2.0) from their first examination. In these 5033 subjects, significantly positive correlations were observed between weight gain between the first and second examinations and harmful changes in MetS components (increased systolic and diastolic blood pressure, TG and glucose and decreased HDL cholesterol; all *P*<0.0001). Highest tertile of PF change was significantly associated with incident NAFLD in both overweight (HR=1.8; 95% CI, 1.2-2.6; *P*<0.001) and obese groups (HR=1.9; 95% CI, 1.3-2.7; *P*<0.001).

Conclusions: High baseline level or increase during follow-up of percentage fat mass was associated with increased risk of NAFLD development over time in lean, overweight and obese population. Lifestyle intervention to reduce fat mass as well as to increase in relative skeletal mass may be needed in lean population to prevent new NAFLD.

Keywords: Fatty liver, Longitudinal study, Body composition, Risk factor

3. Liver Cancer,Basic

O-013

MicroRNA-148a-5p Attenuates the Expression of CD44 and Suppresses Epithelial-Mesenchymal Transitions in Hepatocellular Carcinoma

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Aims: CD44 have known as important modulators of epithelial-mesenchymal transition (EMT) together with transforming growth factor beta1 (TGF-ß1). Moreover, CD44 and TGF-ß1 double positive more enhanced cancer stem cell characteristics acquisition, EMT, and metastasis. This study aimed to investigate the role of miR-148a-5p regulating the EMT as well as CD44/TGF-ß1 in HCC.

Methods: We sorted $CD44^-$ and $CD44^+$ liver cancer stem cells by fluorescence-activated cell sorting (FACs) in TGF-ß1-positive SNU-368 cells and TGF-ß1-negative SNU-354 cells. The miRNAs expression profiles of CD44 sorted cells and TGF-ß1–treated SNU-354 cells were analyzed through next-generation sequencing (NGS). miR-148a-5p mimic and inhibitors were transfected into HCC cells. The expression of mRNA and protein were detected by quantitative real-time PCR (qRT-PCR) and western blot.

Results: FACS analysis showed high expression of CD44 in two HCC cell lines with different levels of TGF-ß1 expression. SNU-354 $CD44^+$ cells with no TGF-ß1 expression only showed increased N-cadherin expression, with no significant changes in E-cadherin expression. However, TGF-ß1-stimulated SNU-354 cells ($CD44^+$/TGF-$ß1^+$) and SNU-368 $CD44^+$ cells exhibited lower E-cadherin and higher N-cadherin. We identified different miRNAs between two groups (SNU-354 $CD44^-$ vs $CD44^+$ cells and SNU-354 con vs TGF-ß1-treated cells), among which miR-148a-5p expression level was up-regulated in SNU-354 $CD44^+$ cells and was down-regulated in TGF-ß1-stimulated SNU-354 cells. Similarly, miR-148a-5p expression was also down-regulated in SNU-368 $CD44^+$ cells ($CD44^+$/TGF-$ß1^+$). The loss of miR-148a-5p in SNU-354 ($CD44^+$/TGF-$ß1^-$) cells showed reduced E-cadherin and increased N-cadherin. In contrast, overexpression of miR-148a-5p in SNU-368 ($CD44^+$/TGF-$ß1^+$) cells reduced mesen-

chymal marker and cell migration as well as down-regulation of CD44. Also, TGF-ß1 stimulation after miR-148a-5p overexpression induced neither the mesenchymal phenotype nor cell migration in SNU-354 cells.

Conclusions: We identified CD44/TGF-ß1-related miRNAs and among them, miR-148a-5p have been confirmed to regulate EMT. The results suggest that CD44/TGF-ß1-regulated miR-148a-5p may serve as specific biomarkers and therapeutic targets for HCC.

Keywords: CD44, Transforming growth factor beta1 (TGF-beta1), Epithelial-mesenchymal transition (EMT), Hepatocellular carcinoma (HCC), miR-148a-5p

O-014

MAGE-1-Targeting Aptamer Inhibits Hepatocellular Carcinoma Cell Growth via PFKFB4 Suppression and ROS Overproduction

Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Yoon Jun Kim[1], Eun Ju Oh[2], Jong In Kim[2], Jong Hun Im[2], Jung Hwan Lee[2], Jung-Hwan Yoon[1*]

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Aims: Aptamers are short synthetic oligomers that bind to protein targets on cancer cells. The melanoma antigen-1 (MAGE-1), a member of MAGE gene family which encode tumor-specific antigens for autologous cytotoxic T cell recognition, is highly expressed in hepatocellular carcinoma (HCC) suggesting the possibility as a novel therapeutic target. We generated aptamers targeting MAGE-1 and assessed those therapeutic potentials in the treatment of HCC.

Methods: MAGE-1 expression on the surface of HCC cells (SNU-761, Huh7, and SNU-3058) was assessed by immunofluorescence staining. Flow cytometry was performed to determine the binding affinity of the MAGE-1 aptamers, which were synthesized through systematic evolution of ligands by exponential enrichment (SELEX) method, to HCC cells. Cell proliferation was analyzed using the MTS assay.

Results: MAGE-1 was highly expressed on the surface of SNU-761, Huh7, and SNU-3058 cells. Ten SELEX-derived MAGE-1 aptamers were evaluated by flow cytometry for selection of high-affinity aptamers to HCC cells. Among MAGE-1 aptamers analyzed, one which showed high affinity to SNU-3058 cells (HCC cell line derived from hypovascular HCC), was selected for MTS assay. MAGE-1 aptamer treatment suppressed HCC cell growth compared to control aptamer. In a microarray, PFKFB4 gene expression was reduced by MAGE-1 aptamer treatment with a –1.77-fold change in SNU-3058 cells. Knockdown of PFKFB4 in cancer cells is known to be associated with reactive oxygen species (ROS) production and cell death. Suppression of PFKFB4 expression after MAGE-1 aptamer treatment in SNU-3058 cells was confirmed by real-time polymerase chain reaction. ROS production was increased by treatment of MAGE-1 aptamer or transfection of PFKFB4 siRNA.

Conclusions: We demonstrated that newly developed MAGE-1 aptamer can bind to HCC cells with high affinity and inhibit HCC cell proliferation via PFKFB4 gene suppression and ROS overproduction. Further investigation of MAGE-1 aptamer as a novel targeted therapy for HCC is needed.

Keywords: MAGE-1, Aptamer, HCC, Liver cancer, PFKFB4, ROS

O-015

Kinase Suppressor of Ras 1 Promotes Development of TAZ-Mediated Intrahepatic Cholangiocarcinoma

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Aims: Liver cancer is a major cause of cancer-related deaths worldwide, of which Intrahepatic cholangiocarcinoma (ICC) is the second most common malignant tumor. Kinase suppressor of ras 1 (KSR1) is a scaffold protein for the RAF-MEK-ERK cascade and promotes phosphorylation of MAPK and ERK kinase (MEK) by RAF. In this study, we have investigated the role of KSR1-dependent signaling pathways in YAP/TAZ-mediated hepatic carcinogenesis.

Methods: Transposons were constructed encoding KSR1 and an activated from of TAZ (TAZ^{S89A}). Transposons were hydrodynamically delivered to livers of 5-week-old C57BL/6 mice. Mice were monitored at least twice per week and sacrificed when moribund. Tumor-bearing livers were formalin fixed for hematoxylin–eosin staining and immunohistochemistry.

Results: Analysis of gene expression levels in human ICC samples deposited in The Cancer Genome Atlas (TCGA) revealed that KSR1 was significantly upregulated in human ICC, compared with non-tumoral surrounding livers ($P<0.01$). Furthermore, simultaneous expression of KSR1 and an activated form of TAZS89A promoted tumorigenesis in mice liver. Histological analysis revealed that these tumors were ICCs, as also indicated by strong immunoreactivity for the CK19 and EpCAM. Interestingly, western blotting of the ICC tissues showed that AKT1 phosphorylation was higher than in normal tissue control, and was positively correlated with KSR1 expression.

Conclusions: KSR1 has been known as a positive regulator of MAPK signaling. In this study, we found a new function of KSR1 that induces activation of AKT signaling. KSR1 promotes TAZ-mediated liver tumorigenesis, and is a key molecule in ICC as a positive regulator of AKT signaling.

Keywords: Intrahepatic cholangiocarcinoma, KSR1, YAP/TAZ, Tumorigenesis

O-016

Loss of ARID1A Serves as Prognostic Biomarker for Hepatocellular Carcinoma and Has Synthetic Lethality with PI3K/mTOR Inhibition

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Aims: Based on the recent study from The Cancer Genome Atlas (TCGA) project, *ARID1A* was one of the most frequently mutations in hepatocellular carcinoma (HCC). Since clinical significance of *ARID1A* in HCC is not clarified despite its high prevalence, the role of *ARID1A* was evaluated.

Methods: By analyzing the gene expression of livers from *Arid1a*-knockout mice, a hepatic *Arid1a*-specific gene expression signature was identified (P<0.05 and $\log_2$ ratio >0.5 fold difference). From this signature, a prediction model was developed to identify tissues lacking *Arid1a* activity and was applied to gene expression data from three independent cohorts of HCC patients to stratify patients according to *ARID1A* activity. The molecular features associated with loss of *ARID1A* were analyzed using TCGA multi-platform data, and Ingenuity Pathway Analysis (IPA) was done to uncover potential signaling pathways associated with *ARID1A* loss. Sensitivity of *ARID1A*-wild-type, -deficient, and -knockout HCC cells to PI3K/mTOR inhibitor GSK2126458 was tested.

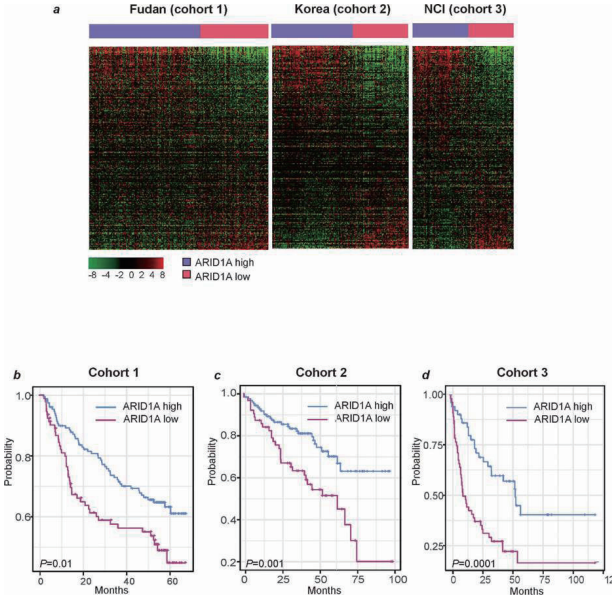

Figure 1.

Results: *ARID1A* inactivation was clinically associated with poor prognosis in all three cohorts and was consistently related to poor prognosis subtypes associated with previously reported gene signatures (high NCI proliferative, hepatic stem cell, silence of Hippo pathway, and SNUR high recurrence). Immune activity, indicated by significantly lower IFNG6 and cytolytic activity scores and enrichment of regulatory T-cell composition, was lower in the *ARID1A*-low subtype. IPA results revealed PI3K/mTOR as activated upstream regulators of the *ARID1A* signature. Sensitivity to GSK2126458 was significantly higher in *ARID1A*-deficient and -knockout cells than in *ARID1A*-wild-type cells (P<0.05).

Conclusions: ARID1A inactivation is significantly associated with poor prognosis and activation of the PI3K/mTOR pathway. ARIDA1A status could be used for identification of HCC tumors sensitive to PI3K/mTOR inhibition.

Keywords: ARID1A, Hepatocellular carcinoma, Genomics, Survival

O-017

Identification of the Novel Exosomal Protein Markers of Hepatocellular Carcinoma

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Aims: The marker of hepatocellular carcinoma-derived exosomes (HEX) is not yet fully identified. In this study, we tried to reveal novel biomarker of hepatocellular carcinoma (HCC) by identifying the specific protein markers of HEX.

Methods: Exosomes were isolated from human HCC cell lines (Hep3B and Huh-7) and immortalized normal hepatocyte cell line (THLE-2). Proteomic analysis was performed for screening the overexpressed proteins in HEX compared to exosome derived normal hepatocyte. To select potential candidate of novel protein maker of HEX among the screened overexpressed protines of HEX, various public data set including TCGA, ICGC, and GSE77314 were analyzed. To validate clinical implication of the selected proteins, serum ELISA was performed in the cohort of liver disease including 22 HCC patients and 22 chronic liver disease patients without HCC.

Results: A total of 757 differentially expressed spots in HEX were identified by deep sequencing. Among them, 54 spots overexpressed more than 2 folds in HEX compared to normal hepatocyte-derived-exosome were selected and purified. ID conversion by using DAVID software were performed for naming the spots. As a result, 22 overexpressed exosomal proteins in HCC cell lines were identified. To select final candidates, the expression level of the 22 candidate proteins were analyzed in various public database and 4 proteins were finally selected as the potential novel protein marker of HEX. Serum ELISA was performed to validate whether these 4 potential HEX protein markers could distinguish HCC patients in an independent co-

hort of liver disease. Among 4 candidate proteins, 2 proteins (HEX_marker1 and HEX_marker2) showed excellent diagnostic performance for distinguish HCC from the patients without HCC by using serum ELISA. (HEX_marker1, AUC=0.936, HEX_marker2, AUC=0.963).

Conclusions: In conclusion, this study revealed 2 potential novel serum protein markers of HEX HCC by using proteomic analysis of HEX.

Keywords: Hepatocellular carcinoma, Exosome, Protein, Biomarker

O-018

Establishment of Tyrosine Kinase Inhibitors-Resistant Murine Hepatocellular Carcinoma *in Vivo* Models and Identification of Resistance-Associated Pathways

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Aims: Tyrosine kinase inhibitors (TKIs) play an important role in the latest treatment of advanced hepatocellular carcinoma (HCC). Despite the fact that lenvatinib and regorafenib as multiple target receptor tyrosine kinase inhibitors showed statistically significant non-inferiority over sorafenib and survival advantages in progressive HCC patients on sorafenib treatment, respectively, those also acquire resistance to both drugs in long-term treatment. We aimed to establish lenvatinib and regorafenib resistance *in vivo* models and to investigate those molecular genetic features that affect resistance of both drugs.

Methods: RIL-175 HCC cells ($2X10^6$) were injected subcutaneously into the C57BL/6 mice. When the average volume of tumors reached to 300 mm^3, mice were randomly divided into 3 groups and received the following treatments: 1) vehicle control, 2) lenvatinib (5 mg/kg/day, PO) and 3) regorafenib (10 mg/kg/day, PO). Tumors were monitored 3 times per week by using Vernier caliper measurement of length (L) and width (W) of the tumor. Tumors volume increase more than 30% in 3 days, reached to 900 mm^3 (for at least 15 days) were considered end points. Total RNA samples were extracted from xenograft tissue and subjected to gene expression anlaysis using Affymetrix Clariom-S Array.

Results: The result of microarray analyses showed that there were 31 statistically significant molecules in the lenvativinb resistance model and 81 molecules in regorafenib resistance model. There were equally significant changes in genes involved in metabolism, human disease, and environmental information processing in both groups which were distinguished from genes related focal adhesion in the lenvatinib resistance group and choline metabolism in cancer, MAPK signaling pathway, and renin secretin in the regorafenib resistance group. Moreover, three molecules of the highest signal intensities (volume) in each group were Adh7, Gstm1 and Mgst1 in the lenvatinib resistance model (Table 1) and Gsta4, Gsta2 and F2r in the regorafenib resistance model (Table 2).

Table 1. Top 3 key molecules for lenvatinib resistance in microarray assay

Gene symbol	Gene ID	Fold change	DEG*	Volume	*P* value
Adh7	11529	-2.917474	Downregulated	7.373720	<0.001
Gstm1	14862	-2.063645	Downregulated	7.484585	0.010
Mgst1	56615	-2.475955	Downregulated	6.905016	<0.001

*Differentially expressed genes

Table 2. Top 3 key molecules for regorafenib resistance in microarray assay

Gene symbol	Gene ID	Fold change	DEG*	Volume	*P* value
Gsta4	14860	1.792794	Upregulated	10.653581	0.002
Gsta2	14858	2.505711	Upregulated	9.560105	<0.001
F2r	14062	-1.874681	Downregulated	9.445315	0.003

*Differentially expressed genes

Conclusions: Our study well-established lenvatinib and regorafenib resistance *in vivo* models and identified potential key molecules in both resistance HCC cells. The pathways that play an important role in the resistance mechanism of lenvatinib and regorafenib might be different. Further studies are needed to overcome resistance mechanisms to both drugs.

Keywords: Hepatocellular carcinoma, Lenvatinib resistance, Regorafenib resistance, *In vivo* model

4. Cirrhosis & Liver Failure

O-019

Generation of Induced Secretome from Adipose-Derived Stem Cells Specialized for Disease-Specific Treatment: An Experimental Mouse Model

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Aims: Recently, the exclusive use of mesenchymal stem cell (MSC)-secreted molecules, named as the secretome, rather than cells has been evaluated for overcoming the limitations of cell-based therapy while maintaining its advantages. The goal of this study was to improve cell-free therapy by adding disease-specificity through stimulation of MSCs using disease-causing materials.

Methods: We collected the secretory materials (named as inducers) released from AML12 hepatocytes that had been pretreated with thioacetamide (TAA) and generated the TAA-induced secretome (TAA-isecretome) after stimulating adipose-derived stem cells (ASCs) with the inducers. The TAA-isecretome was intravenously administered to mice with TAA-induced hepatic failure and those with partial hepatectomy.

Results: TAA-isecretome infusion showed higher therapeutic

potential in terms of (a) restoring disorganized hepatic tissue to normal tissue, (b) inhibiting proinflammatory cytokines (interleukin-6 and tumor necrosis factor-a), and (c) reducing abnormally elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase) compared to the naïve secretome infusion in mice with TAA-induced hepatic failure. However, the TAA-isecretome showed inferior therapeutic potential for restoring hepatic function in partially hepatectomized mice.

Conclusions: Our results suggest that appropriate stimulation of MSCs with disease-causing agents leads to the production of a secretome specialized for treating a specific disease. Additionally, isecretome therapy is expected to open a new way of developing various specific therapeutics based on the high plasticity and responsiveness of MSCs.

O-020

Clinical Impact of Circulating Exosomal microRNA as a Novel Biomarker of Liver Fibrosis

Young Chang[1], Jae Young Jang[1]*, Tom Ryu[1], Han Seul Park[1], Soung Won Jeong[1], Jeong-Ju Yoo[3], Sae Hwan Lee[2], Sang Gyune Kim[3], Young Seok Kim[3], Hong Soo Kim[2], So Young Jin[4], Seongho Ryu[5]

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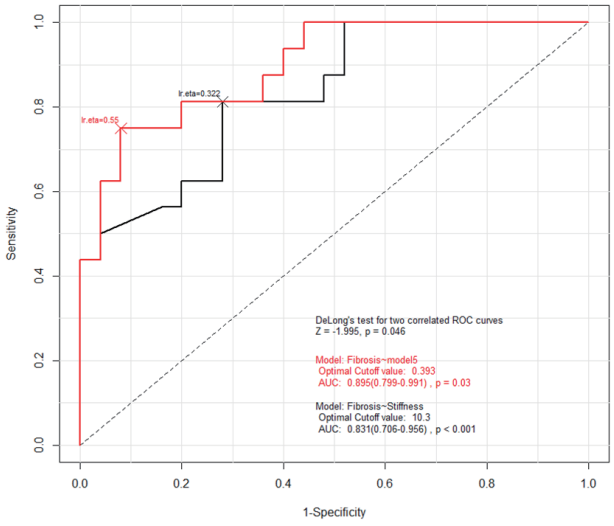
Aims: Many approaches have been suggested to diagnose liver fibrosis non-invasively including various serum biomarkers and ultrasound-based elastography, but none of them have yet to replace liver biopsy. Circulating microRNA (miRNAs) have been suggested as possible diagnostic tools for liver diseases in various circumstances. We investigated whether circulating exosomal miRNAs associated with liver fibrosis and its clinical impact as a biomarker of liver fibrosis.

Methods: This study prospectively enrolled a total of 85 patients who underwent liver biopsy in three large-volume hospitals in Korea. Exosome was extracted from the serum samples followed by quantification of exosomal miRNAs using targeted RT-qPCR. A novel model to discriminate advanced fibrosis using miRNA level was derived by multivariate logistic regression. The performance of the models were evaluated and compared by area under the ROC curve (AUC) and DeLong's test.

Results: The level of miR-122 and miR-194 decreased as the pathologic fibrosis stage progressed 0 to 4. Patients with biopsy-proved advanced fibrosis showed significantly lower level of miR-122 (P<0.001) and miR-194 (P=0.073) than those without advanced fibrosis. miR-122 exhibited a fair performance in discriminating advanced fibrosis with AUC of 0.77. When combined with Fibrosis-4 score (FIB-4) and transient elastography (TE), miR-122 represented improved discrimination function with AUC of 0.86, which was higher than any other non-invasive modalities including TE alone (AUC of 0.80). In subgroup patients who had non-viral etiology of liver disease, the performance of miR-122 was better than that of whole study population with AUC of 0.87. Furthermore, the combination model of miR-122, FIB-4 and TE showed the best discrimination function with AUC of 0.90, which was significantly higher than that of TE alone (AUC, 0.83; DeLong's test P=0.046).



Conclusions: Circulating exosomal miR-122 can serve as a novel biomarker in discriminating advanced liver fibrosis especially combined with other non-invasive tests such as FIB-4 and TE.

Keywords: Exosome, MicroRNA, Fibrosis, Biomarker

O-021

New Therapeutic Strategies for Hepatic Fibrosis Using Stem Cell Printing Three-Dimensional Liver Patch

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Aims: Liver cirrhosis is a major source of liver cancer which is the leading cause of death worldwide. Mesenchymal stem cell (MSC) therapy is being used as a liver transplant alternative therapy in liver cirrhosis patients. However, MSC therapy has a low delivery efficiency. Therefore, to overcome this problem, we established a patch-shaped cell therapy agent (liver patch)

containing mesenchymal stem cells through a three-dimensional cell-printing technique for anti-fibrosis therapy.
Methods: We established the liver patch structure through human bone marrow-derived mesenchymal stem cells (BMMSCs) encapsulated bioink (liver patch).
In vitro experiment: The activated hepatic stellate cell line, LX2 was co-cultured with liver patch. The expression of fibrosis markers, Gli3, COL1A1, Desmin, Vimentin, and a-SMA were measured by qRT-PCR and Western blot.
In vivo experiment: After modeling the fibrotic mice through thioacetamide (TAA) injection, the mice were separated into four groups; negative control, intravascular injection of hBMMSC cells, only liver patch (without hBMMSC) and hBMMSC-encapsulated liver patch. All hBMMSC cells were labeled with RFP. Hydroxy proline and Sirius red assay were used to measure the collagen deposition.
Results: The ability of hBMMSC differentiation was improved in the hBMMSC-encapsulated liver patch. Co-culture of the liver patch with activated LX2 cells decreased the expression of fibrosis markers. In fibrotic mice model, the RFP-labeled hBMMSC was observed up to 25 days in the liver of hBMMSC-encapsulated patch group, but comparative group has no fluorescence was observed. Moreover, hBMMSC-encapsulated liver patch implanting fibrosis mice decreased collagen deposition and expression of fibrosis markers.
Conclusions: Based on these results, we intend to upgrade liver patches through a complex patterning structure with vascular endothelial progenitor cells to improved delivery efficiency and survival rate of mesenchymal stem cells. We present this liver patch as a promising candidate for fibrosis treatment of a new therapeutic strategy for liver fibrosis.
This research was supported by BrainKorea 21.
Keywords: Liver fibrosis, Mesenchymal stem cell therapy, 3D-cell printing, Stem cell

O-022

Development of a Prognostic Score to Predict Mortality in Patients with Pediatric Acute Liver Failure

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Aims: The aim of this study was to develop a new prognostic score based on change in serial laboratory data in patients with pediatric acute liver failure (PALF).
Methods: We retrospectively collected data on patients with PALF at the Seoul National University Children Hospital (SNUCH) and the Asan Medical Center (AMC). Daily morning laboratory records were obtained for up to 7 days after diagnosis of PALF; (1) total bilirubin (TB) (mg/dL), international normalized ratio for prothrombin time (INR) at enrollment (2) peak TB, peak INR, peak ammonia (mmol/L) (3) a) the difference between the peak TB and TB at enrollment (i.e., ⊿peak TB), b) the difference between the peak INR and INR at enrollment (i.e., ⊿peak INR), c) the maximum change in serial TB (i.e., ⊿daily TB), d) the maximum change in serial INR level (i.e., ⊿daily INR).
Results: 42 patients of derivation cohort (SNUCH) and 33 patients of validation cohort (AMC) were enrolled. Multivariate logistic regression was conducted to predict death in derivation cohort and a new score was developed. PALF-Delta score (PALF-Ds) = [0.232 * ⊿peak TB (mg/dL)] + [2.267 * ⊿daily INR] + [0.01 * peak ammonia (mmol/L)] - 4.514. PALF-Ds showed excellent accuracy in both cohort with AUC 0.922 in derivation cohort (sensitivity 81%, specificity 91%) and AUC 0.951 in validation cohort (sensitivity 93%, specificity 90%).
Conclusions: A prognostic scoring system using the change of TB/INR might be useful for predicting death in patients with PALF.
Keywords: Pediatric acute liver failure, Prognostic score

O-023

Postoperative Hepatic Decompensation in Patients with Cirrhosis Undergoing Major Surgery: Prognostic Value of Liver Stiffness

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Aims: Patients with liver cirrhosis are at fear of postoperative hepatic decompensation, despite the need for significant surgery. This prospective study investigated the prognostic value of liver stiffness measurement (LS) for predicting the development of hepatic decompensation after major surgery requiring general anesthesia.
Methods: This prospective study enrolled 132 consecutive patients with compensated liver cirrhosis (Child-Pugh Class A) who underwent a preoperative liver stiffness (LS) measurement and major surgery between Jan 2016 to September 2018. Definition of hepatic decompensation included at least one sign of liver function impairment (jaundice, ascites, hepatic encephalopathy, or coagulopathy). Predictors of hepatic decompensation were assessed with logistic regression analysis.
Results: Seventy four (56.1%) patients had hepatitis B virus infection and 123 (93.2%) patients had Child-Pugh score 5. The mean LS value was 14.0 kPa. Thirteen (9.8%) patients had hepatic decompensation after major surgery. LS value, and Child-Pugh score were significantly associated with hepatic decompensation in the univariate analysis, but LS value was the only significant predictor in subsequent multivariate analysis (cutoff, 15.0 kPa; *P*=0.001; odds ratio; 36.3; 95% confidence interval, 4.4–300.4).

The mean LS value of patients with hepatic decompensation was significantly higher than that of patients without hepatic decompensation after surgery (26.3 kPa vs. 12.7 kPa, *P*<0.001).

Conclusions: Patients with compensated cirrhosis had relatively low risk for hepatic decompesation after major surgery. LS value may be useful for predicting the development of postoperative hepatic decompensation.

Keywords: Cirrhois, Hepatic decompensation, Liver stiffness, Major surgery

O-024

Clinical Application of New EASL Clinical Practice Guideline for Malnutrition in Cirrhosis Patients

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Department of Internal Medicine, University of Hanyang College of Medicine, Korea

Aims: Recently, clinical practice guideline for nutritional evaluation of cirrhosis patients developed by European Association for the Study of the Liver (EASL). We tried to apply nutrition assessment according to the EASL Clinical Practice Guideline to clinical practice and analyzed the prevalence of malnutrition and its association with related factors.

Methods: From April, 2018 to January, 2019, 309 patients who visited liver clinic in Hanyang University Hospital were enrolled. Sarcopenia was assessed by hand strength measurement and bioelectrical impedence analysis. Subjective global assessment (SGA) and dietary intake assessment was performed. Based on these, malnutrition was defined according to the EASL Clinical Practice Guideline. Cohen's kappa analysis was used to calculate the degree of agreement between the two groups in which malnutrition was diagnosed by different methods.

Results: The prevalence of malnutrition diagnosed according to the EASL clinical guideline was 34.0% and there was no difference by etiology. The prevalence of sarcopenia was 5.5%, malnutrition assessment by SGA was 13.6%, and impaired dietary intake was 27.5%. The prevalence of malnutrition was increased according to disease severity (Child A; 31.3%, Child B; 41.4%, Child C; 71.4%) (*P*=0.006). Lower body mass index (BMI ≤ 18.5 kg/m^2; 60.0%, BMI ≥ 18.5 kg/m^2 & < 25 kg/m^2; 33.9%, BMI ≥ 25 kg/m^2; 32.8%) showed relationship with greater prevalence of malnutrition, but no statistically significant. The prevalence of malnutrition was 72.4% in patients intake protein less than 1.0g/kg. Low protein intake and severe disease activity are confirmed to risk factor of malnutrition in multi-variant analysis.

Conclusions: Prevalence of malnutrition in cirrhosis patients diagnosed by EASL clinical practice guideline was 34.0%, and there was no difference by etiology. Low protein intake and severe disease activity are independent risk factors for malnutrition.

Keywords: Liver cirrhosis, Malnutrition, EASL guideline

5. HCV

O-025

Cost-Effectiveness of Screening and Treatment of All Korean Chronic Hepatitis C Patients

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Background/Aim: To investigate the cost-effectiveness of screening with subsequent direct-acting antiviral (DAA) treatment for all chronic hepatitis C (CHC) patients in South Korea in patients aged 40 and older as compared to the current practice of screening high-risk patients only.

Methods: A published Markov model was used in conjunction with a screening and treatment decision tree to model CHC patients, aged 40-49, 50-59, 60-69, and 70 and older, to evaluate the cost-effectiveness of a 'screen-all' vs. 'high-risk' only screening strategy followed by treatment. Only 16.1% were screened in the 'high-risk' scenario. 87.6% and 12.4% of patients were non-cirrhotic and compensated cirrhotic, respectively. CHC patients were distributed across genotypes 1 (53.6%) & 2 (46.4%). Across all cohorts, 72% of patients were assumed to accept screening and 63.7% of HCV RNA-positive patients were assumed to accept treatment. Upon accepting screening as well as treatment, patients were treated either with ledipasvir/sofosbuvir (LDV/SOF), SOF+ribavirin (SOF+RBV; GT2 only), or glecaprevir/pibrentasvir (GLE/PIB). Model inputs were sourced from published literature and costing databases, and validated by Korean hepatologists.

Table 1. Health and Economic Outcomes of Screening and Treatment Strategies in South Korea

	NO SCREENING	RISK-BASED SCREENING			SCREEN ONCE			SCREEN TWICE		
GT1 TREATMENT	N/A	LDV/SOF	LDV/SOF	GLE/PIB	LDV/SOF	LDV/SOF	GLE/PIB	LDV/SOF	LDV/SOF	GLE/PIB
GT2 TREATMENT	N/A	LDV/SOF	SOF+RBV	GLE/PIB	LDV/SOF	SOF+RBV	GLE/PIB	LDV/SOF	SOF+RBV	GLE/PIB
CC	8,264	7,691	7,690	7,676	4,703	4,700	4,615	4,155	4,152	4,056
DCC	5,929	5,571	5,571	5,567	3,705	3,706	3,679	3,400	3,402	3,372
HCC	15,555	14,538	14,541	14,531	9,241	9,262	9,200	8,330	8,354	8,284
LT	64	60	60	60	40	40	40	37	37	36
EM	16,530	15,466	15,469	15,457	9,919	9,935	9,866	9,015	9,033	8,955
SCREENING COSTS	₩0.0 bn	₩9.8 bn	₩9.8 bn	₩9.8 bn	₩73.7 bn	₩73.7 bn	₩73.7 bn	₩82.7 bn	₩82.7 bn	₩82.7 bn
TREATMENT COSTS	₩0.0 bn	₩39.9 bn	₩40.2 bn	₩46.7 bn	₩247.8 bn	₩249.6 bn	₩290.3 bn	₩276.3 bn	₩278.1 bn	₩323.3 bn
TOTAL COSTS	₩479.0 bn	₩528.4 bn	₩529.1 bn	₩535.1 bn	₩799.1 bn	₩803.4 bn	₩840.2 bn	₩820.3 bn	₩824.6 bn	₩865.7 bn
QALYs	548,626	558,097	558,071	558,166	607,449	607,287	607,879	612,490	612,309	612,949
LYs	708,947	716,738	716,730	716,817	757,338	757,290	757,832	760,873	760,820	761,401
ICER (vs. NO SCREEN)	*REFERENCE*	₩ 5,225,670	₩ 5,313,714	₩ 5,881,769	₩ 5,441,771	₩ 5,530,414	₩ 6,096,301	₩ 5,344,496	₩ 5,428,162	₩ 6,012,035
ICER (vs. RISK-BASED SCREEN)	N/A	*REFERENCE*	DOMINATED	₩ 95,567,165	₩ 5,483,240	₩ 5,589,086	₩ 6,261,927	₩ 5,365,185	₩ 5,463,536	₩ 6,147,804
ICER (SCREEN ONCE vs. SCREEN TWICE)	N/A	N/A	N/A	N/A	*REFERENCE*	DOMINATED	₩ *95,567,165*	₩ *4,209,357*	₩ *5,263,443*	₩ *12,111,031*
							ICER (WITHIN SCREEN TWICE)	*REFERENCE*	DOMINATED	₩98,845,537

Key: CC, compensated cirrhosis; DCC, decompensated cirrhosis; EM, extra mortality; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LDV/SOF, ledipasvir/sofosbuvir; LT, liver transplant; LY, life-years; QALY, quality-adjusted life-years; RBV, ribavirin

Results: Risk-based screening was found to be cost-effective vs. no screening for any DAA scenario (Table 1). Screening once was found to be cost-effective vs. risk-based screening for any DAA scenario. Screening twice is cost-effective compared to screening once for any DAA scenario. When comparing

within all screening scenarios using LDV/SOF for all GT's as reference, LDV/SOF dominates (i.e., is more effective and less costly) LDV/SOF in GT1 and SOF+RBV in GT2. Assuming a willingness-to-pay threshold of 1xGDP per capita (₩36,415,909/QALY), GLE/PIB is less cost-effective in any scenario vs. LDV/SOF.

Conclusions: Screening all South Korean patients once or twice followed by DAA treatment is cost-effective compared to high-risk screening. Treating with LDV/SOF in all GT's was a dominant strategy compared to SOF+RBV. GLE/PIB is less cost-effective strategy than LDV/SOF.

Keywords: Cost effectiveness, Screening, HCV, Screening and treatment

O-026

Preliminary Efficacy and Safety of 8-Week Glecaprevir/Pibrentasvir in Patients with HCV Genotype 1–6 Infection and Compensated Cirrhosis: The EXPEDITION-8 Study

Robert S Brown Jr[1], Christophe Hezode[2], Stanley Wang[3], Maria Buti[4], Wan-Long Chuang[5], Humberto Aguilar[6], Gábor Horváth[7], Barbara Rosado Carrion[8], Federico Rodriguez-Perez[9], Eric Cohen[3], Yiran B Hu[3], Gretja Schnell[3], Chih-Wei Lin[3*], Lino Rodrigues[3], Roger Trinh[3], Federico J Mensa[3], Franco Felizarta[10], Yongkyun Won[11]

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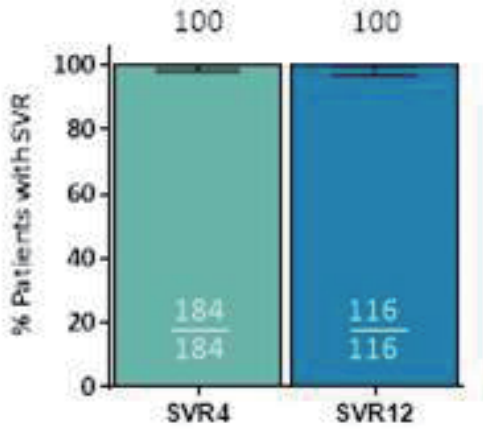
Aims: The pangenotypic direct-acting antivirals glecaprevir (identified by AbbVie and Enanta) coformulated with pibrentasvir (G/P) are approved to treat chronic HCV genotype (GT) 1–6 infection. Eight-week G/P achieved high SVR12 rates in Phase 2 and 3 studies, but was not studied in patients with compensated cirrhosis. Based on the high SVR12 rates demonstrated in treatment-naïve patients with HCV GT1-6 infection and compensated cirrhosis treated with 12-week G/P, this study evaluates the efficacy and safety of an 8-week G/P treatment duration in that population.

Methods: EXPEDITION-8 is an ongoing phase 3, non-randomized, single arm, open-label, multicenter study conducted in adults with chronic HCV GT1–6 infection with compensated cirrhosis who are HCV treatment-naïve. A recently approved protocol amendment enabled the inclusion of HCV GT3-infected patients, who are not included in this analysis. G/P (300 mg/120 mg) is being dosed orally once-daily with food for 8 weeks. The primary efficacy endpoint is the SVR12 rate. Secondary endpoints are on-treatment virologic failure and relapse rates. Adverse events and clinical laboratory abnormalities are being monitored in all patients.

Results: In total, 280 treatment-naïve patients with compensated cirrhosis have enrolled and are included in the analysis. The majority of patients were white (80%), male (60%), and with a Child-Pugh score of 5 (90%); the distribution of genotypes were as follows: GT1 (82%), GT2 (9%), GT4 (5%), GT5 (<1%), and GT6 (3%). At baseline, median and range values for key characteristics were as follows: HCV RNA 6.3 (3.4–7.5) $\log_{10}$ IU/mL, FibroScan score 20.7 (2.5–70.6) kPa, platelet count 152 (42–788) × 10^9 cells/L, total bilirubin 0.7 (0.2–2.4) mg/dL and albumin 4.2 (2.7–5.1) g/dL. To date, 116 patients have completed the post-treatment week 12 visit; Figure 1 shows preliminary efficacy results for those with available post-treatment week 4 and/or 12 data. No virologic failures have occurred. Adverse events (AEs) have been mostly mild, with the most common (at least 5%) AEs being pruritus and fatigue (both 9%), headache (7%) and nausea (6%). No AEs have led to discontinuation of G/P; 5 serious AEs have occurred, none of which were deemed related to G/P.



Conclusions: In this ongoing study, G/P for 8 weeks in treatment-naïve patients with HCV infection and compensated cirrhosis has been well-tolerated and achieved high rates of SVR, with no virologic failures to date. Updated efficacy and safety data will be presented at the meeting.

Keywords: Hepatitis C, Liver cirrhosis, RNA virus infection

O-027

Ledipasvir/Sofosbuvir for 12 Weeks Is Effective in HCV-Infected Asian Patients with Difference Liver Fibrosis Stages: Integrated Analysis of Clinical Studies

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Aims: Ledipasvir (LDV)/sofosbuvir (SOF) fixed-dose combination is approved as a 12-week regimen for patients with HCV genotype 1, 2, 4-6 infection in several Asian countries. This integrated analysis describes the efficacy and safety of LDV/SOF treatment in HCV-infected genotype (GT) 1 and 2 Asian patients across the spectrum of fibrosis stages.

Methods: This is a retrospective analysis from 797 Asian patients with GT 1 or 2 HCV infection treated with LDV/SOF for 12 weeks in 4 phase 3 studies. Fibrosis stages were defined by liver biopsy, transient elastography, or Fibrotest. Efficacy was assessed by sustained virologic response 12 weeks after treatment (SVR12). Safety data was analyzed.

Results: 797 Asian subjects were treated with LDV/SOF for 12 weeks. 56% were female, 70% had IL28B CC genotype, 45% had prior treatment failure and 78% were infected with genotype 1. Overall 68% were F0-F2, 14% were F3, and 18% were F4. In completer analysis, the overall SVR rate was 99% (786/791, 99% [788/796] in Intend-to-treat analysis), and was 99% (617/619) and 98% (169/172) in subject infected with HCV genotype 1 and genotype 2, respectively. The SVR rate was 99% (535/536), 97% (109/112), and 99% (142/143) in subjects with F0-F2, F3, and F4 fibrosis respectively. Among previously treated subjects, the SVR rate was 99% (218/219), 97% (60/62), 99% (77/78) in F0-F2, F3, and F4 subjects respectively. The treatment was well tolerated with 2% (9/796, 6 in F0-F2, 1 in F3 and 2 in F4 subjects) severe adverse events and 0.4% (3 in F0-F2 subjects) discontinuations due to adverse event.

Conclusions: 12 weeks of LDV/SOF treatment is highly efficacious and well tolerated in Asian patients with GT1 and GT2 HCV infection regardless of fibrosis stages.

Keywords: HCV, Asian, Fibrosis, Ledipasvir, Sofosbuvir

O-028

Real World Efficacy and Safety of DAA in Chronic Hepatitis C Patients with Genotype 2 in Korean Population

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Aims: Although the era of direct antiviral agent in the treatment for chronic hepatitis C (CHC) came, options for genotype 2 (G2) have been limited available in Korea. Recently, glecaprevir/pibrentasvir (G/P) was introduced for these patients in addition to sofosbuvir (SOF)+ribavirin (RBV) in clinical practice. At this point, we are intended to investigate the effectiveness and safety of both regimens in CHC G2 Korean patients in real-world setting.

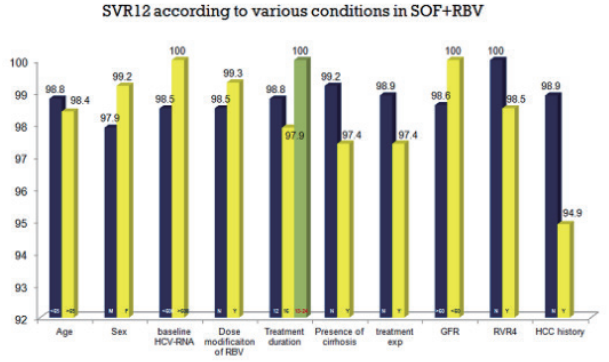
Methods: Seven hundred eighty sixinSOF+RBV and 155 in G/P regimen between Sep 2015 and Feb 2019 in 7 hosopitals in Busan-Ulsan-Gyeognam Province Network were enrolled. Fifty in SOF+RBV and 7 in G/P regimen did not complete treatment due to follow-up loss, adverse effect and self-stopping. Within available data, rapid virologic response at 4 weeks (RVR4), end of treatment response (ETR), sustained virologic response at 12 weeks after treatment (SVR12) and incidence of adverse events were analyzed.

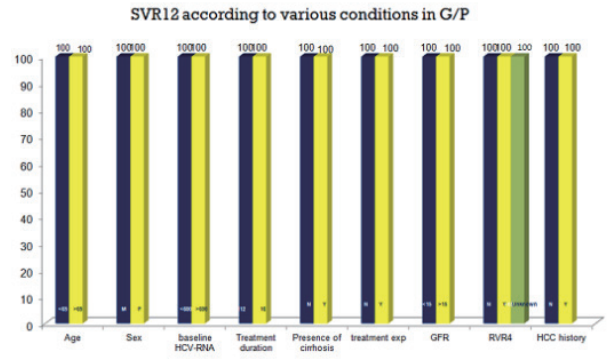
Results: Treatment was completed in 94.6% (n=736) in SOR + RBV group and 95.5% (n=115) in G/P group. The analysis for G/P group was divided into EOT (n=115) and SVR12 group (n=31) because the rest patients (n=84) are waiting for SVR12. Baseline characteristics of the enrolled patients are shown in Figure 1. The median age of the enrolled patients was 61, and 42.4% were male and 57.6% were female. 685 (84.2%) patients were naive and 129 (15.8%) were IFN or DAA experienced. 132 (18.9%) patients were started less than the proposed RBV dose in SOF + RBV group. The percentages of RVR, ETR, and SVR12 were 85.7%, 98.6% and 100% in SOF + RBV group, and 87%, 100% and 100% in G/P group. History of HCC was the only factor associated with SVR12 in SOF + RBV group (P=0.035). SVR12 was analyzed by baseline age, sex, presence of cirrhosis, treatment history, baseline HCV-RNA, RBV dose modification, history of HCC and RVR4. Figure 2 showed SVR12 according to various groups. Nine patients (1.3%) discontinued treatment prematurely due to adverse events in SOF + RBV group. Patients with SOF + RBV showed diverse adverse events and most common AE was anemia (20.3%), followed by gastrointestinal problem (11.4%) and fatigue (10.4%). SOF + RBV group showed significantly higher adverse events than G/P group.

Conclusions: Treatment with SOF + RBV and G/P regimen were both highly effective in Korean hepatitis C patients with GT2 regardless of various condition. However, HCC history was slightly negative effect on treatment outcome and more attention would be paid to adverse events in SOF + RBV group. G/P regimen would be a also good treatment option for patients with chronic hepatitis C in Korea.

Baseline characteristics

	SOF+RBV (SVR12) (n=699)	G/P (EOT) (n=115)	G/P (SVR12) (n=31)
Age	61	61	61
Sex (M/F)	296/403	49/66	14/17
Genotype (2/2a/2b/2c/2a+2c)	88/440/54/1/115	27/63/4//0/21	9/15/2/0/5
Treatment exp (no/IFN/DAA)	580/113/6	105/7/3	26/3/2
Treatment duration (S+R - 12 wk/16 wk/others) (G/P - 8 wk/12 wk)	538/157/4	90/25	25/6
HBV (no/yes)	682/17	113/2	31/0
FL (no/yes)	527/172	79/36	21/10
LC (no/yes)	492/207	89/26	25/6
LC (Child A/B/C)	190/15/2	26/0/0	6/0/0
HCC history (no/yes)	657/42	112/3	30/1
Baseline HCV-RNA	2,513,155	3,417,664	3,449,110
Baseline Hb	14	13	13
Baseline PLT	176	185	174
Baseline Cr	0.95	1.76	1.98
Baseillne GFR	92.08	77.36	71.05
CKD stage (1/2/3/4/5/dialysis)	375/293/30/0/1	50/43/5/2/2/13	10/14/2/0/1/4
Baseline AST	66	57	69
Baseline ALT	61	58	75
Baseline AFP	15.4	11.61	13.74





Keywords: Sofosbuvir, Ribavirin, Glecaprevir/Pibrentasvir, Genotype 2

O-029

Use of Ribavirin for Chronic Hepatitis C Treatment on Direct-Acting Antiviral Era: Real World Practice

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Aims: Ribavirin is still used with DAA, and it is still necessary to monitor the anemia. The aim of this study was to identify factors predictive of anemia during the treatment and to investigate the ribavirin reduction behavior and its effects during the treatment with DAA in the real worlds practice.

Methods: SOF and RBV treatment group from May 2016 to April 2017 and PR treatment group from 2008 to 2012 were enrolled. The medical records of the subjects were analyzed.

Results: There were 221 (93 males and 138 females) in SOF+RBV group and 178 (99 males and 79 females) in PR group, and SVR was 85.15% in PR group and 98.1% in SOF+RBV group. There was no significant difference in incidence of hemoglobin <10 g/dL between the two groups (*P*=0.414). During SOF+RBV treatment, the patients who reduced the dose of ribavirin were 18.9% (40/212): 22 with hemoglobin <10 g/dL, 10 with significant reductions from baseline hemoglobin, 6 due to side effects. Dose reduction of ribavirin was associated with low WBC, ANC, hemoglobin, hematocrit, platelet values, and high MCV values at the beginning of treatment. Ribavirin reduction was associated with low WBC, ANC, hemoglobin, hematocrit, platelet values, and high MCV values at the beginning of treatment. Also, it was associated with cirrhosis, older age, lower BMI, and longer treatment duration. Multivariate analysis showed that only MCV values were associated with ribavirin reduction (*P*=0.010). Accordingly, in the results of verifying the significance of MCV value, the change in MCV values affected SVR on PR group, but it was not associated with SVR in SOF+RBV group. MCV values and its change in the SOF+RBV group were associated with the incidence of anemia and reductions in the ribavirin dose during the treatment.

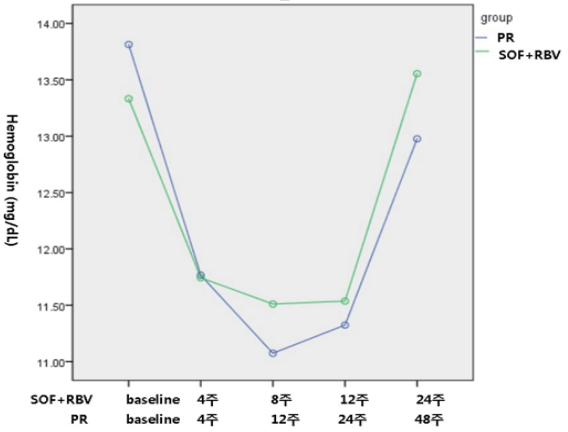

Figure 1A

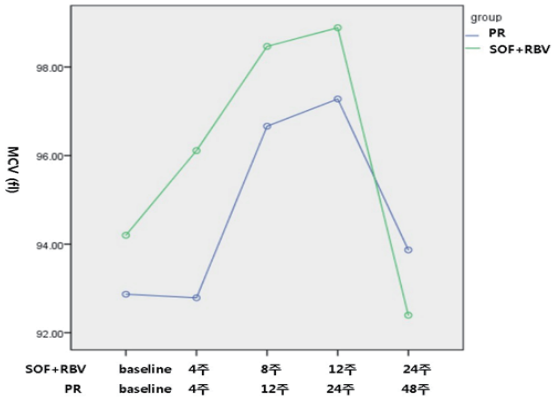

Figure 1B

Conclusions: The incidence of anemia during the treatment with DAA was similar to that with the PR treatment, and the baseline MCV value could predict development of anemia during DAA plus ribavirin treatment. Therefore, patients who haven high baseline values of MCV require close monitoring of anemia during the treatment.

Keywords: Chronic hepatitis C, Sofosbuvir, Ribavirin, Peglyated interferon

O-030

Design and Validation of Risk Prediction Model for Hepatocellular Carcinoma Development after Sustained Virological Response in Patients with Chronic Hepatitis C

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Aims: Hepatocellular carcinoma can develop after hepatitis C virus eradication. We developed a new hepatocellular carcinoma risk score (HCC-SVR score) based on independent predictors for chronic hepatitis C after sustained virological response.

Methods: Between 2003 and 2016, 1193 patients with chronic hepatitis C who achieved sustained virological response through antiviral therapy were included (669 for training cohort, 524 for validation cohort). The HCC-SVR score was developed using multivariate Cox proportional hazards regression modelling.

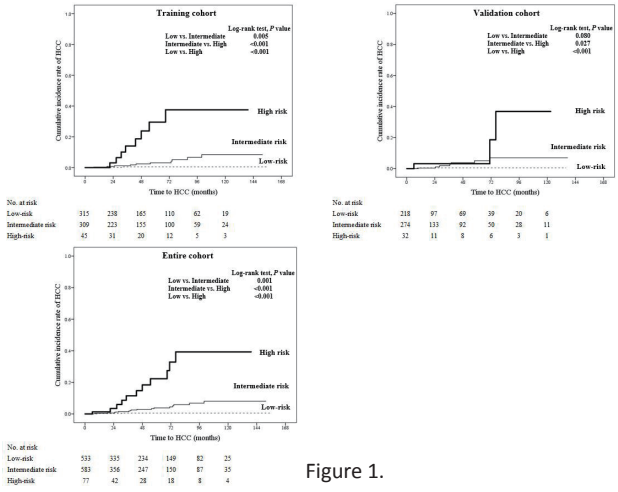

Figure 1.

Table. Independent risk factors for survival and establishment of HCC-SVR score

Risk factors	HR	95% CI	*P* value	Point allocation
Male gender	10.68	2.46-46.29	0.002	3
Alpha-fetoprotein				
< 6.0 ng/mL	1 (reference)			
≥ 6.0 ng/mL	3.30	1.12-9.69	0.030	1
FIB-4				
< 1.45	1 (reference)			
1.45 - 3.25	6.51	0.82-51.42	0.076	2
> 3.25	17.41	2.09-144.83	0.008	5
Risk stratification using HCV-SVR score		Points		
Low-risk		0 - 2		
Intermediate risk		3 - 7		
High-risk		8 - 9		

Results: Hepatocellular carcinoma occurred more frequently in older, male patients and was associated with liver cirrhosis; hypertension; diabetes; lower platelet count; higher alpha-fetoprotein, aspartate, and alanine aminotransferase; lower total cholesterol; and higher fibrosis-4 index (FIB-4) (all $P<0.05$). FIB-4 (hazard ratio = 1.080), male gender (hazard ratio = 8.189), and higher alpha-fetoprotein (hazard ratio = 1.060) independently predicted hepatocellular carcinoma (all $P<0.05$). HCC-SVR score successfully predicted hepatocellular carcinoma development risk (area under receiver operating characteristic curve [AUC] = 0.771, 0.991, and 0.739 at 2, 6, and 10 years, respectively). The cumulative incidence rate of hepatocellular carcinoma differed significantly among groups stratified by HCC-SVR risk score (0–2 points, low; 3–7 points, intermediate; 8–9 points, high risk) (all $P<0.05$ by log-rank test). HCC-SVR score was maintained in a validation cohort (n = 524) (AUC = 0.728 at 2 years, 0.809 at 6 years, and 0.970 at 8 years).

Conclusions: The HCC-SVR score enables risk stratification for hepatocellular carcinoma development at sustained virological

response in patients with chronic hepatitis C.

Keywords: FIB-4, Hepatitis C, Sustained virological response, Hepatocellular carcinoma, Prediction

6. Liver Cancer

O-031

Tumor Marker-Based Characterization of Patients with Intermediate-Stage Hepatocellular Carcinoma Deemed to Have a Grave Prognosis

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Aims: For patients with intermediate-stage hepatocellular carcinoma (HCC), the definition of refractoriness to transarterial chemoembolization (TACE), which might be candidate for systemic therapy, is still controversial. We sought to derive and validate a tumor marker-based algorithm to guide the retreatment of intermediate-stage HCC with TACE.

Methods: The multiple study cohorts comprised a total of 482 consecutive patients who underwent TACE for treatment-naïve intermediate-stage HCC. We derived a prediction model for overall survival (OS) using pre- and post-TACE MoRAL score (i.e., MoRAL score=11×√ protein induced by vitamin K absence-II [PIVKA-II] + 2×√alpha-fetoprotein [AFP]), which was proven to reflect both tumor burden and biologic aggressiveness of HCC in explant liver, from the training cohort (n=193). These results were externally validated in both an independent hospital cohort (from two large-volume centers, n=140) and a Korean National Cancer Registry sample cohort (n=149).

Results: Multivariable analyses indicated that the changes in MoRAL score (ΔMoRAL) after initial TACE was an independent predictor of OS (MoRAL-increase *vs*. MoRAL-non-increase: adjusted hazard ratio [HR]=2.18, 95% confidence interval [CI]=1.37–3.46, *P*=0.001; median OS=18.8 *vs*. 37.8 months) (Figure 1A). In a subgroup of patients with high baseline MoRAL score (≥89.5, 25th percentile and higher), the prognostic impact of ΔMoRAL was more pronounced (MoRAL-increase *vs*. MoRAL-non-increase: HR=3.68, 95% CI=1.54–8.76, *P*<0.001; median OS=9.9 *vs*. 37.4 months) (Figure 1B). These results were reproduced in the two external validation cohorts (Figure 2).

Conclusions: The ΔMoRAL after the first TACE, a simple and objective index, provides refined prognostication for patients with intermediate-stage HCC. Proceeding to a second TACE may not provide additional survival benefit in cases of MoRAL-increase after the first TACE in patients with high baseline MoRAL score (≥89.5) who might be candidates for systemic therapy.

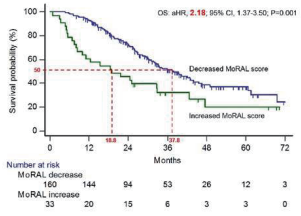

Figure 1A. Prognostic significance of the ΔMoRAL in the training cohort

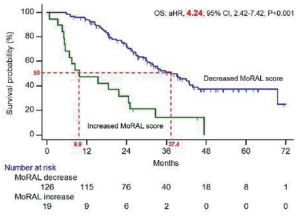

Figure 1A. Prognostic significance of the ΔMoRAL in the training cohort with baseline MoRAL score ≥89.5 (25 percentile value)

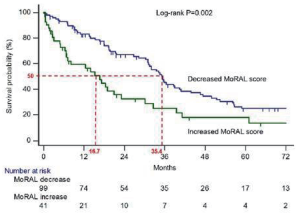

Figure 2A. Prognostic significance of the ΔMoRAL in the validation cohort

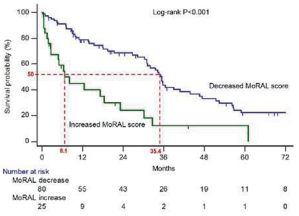

Figure 2A. Prognostic significance of the ΔMoRAL in the validation cohort with baseline MoRAL score ≥89.5 (25 percentile value)

Keywords: Tumor marker, Alpha-fetoprotein, Protein induced by vitamin K absence-II, TACE refractoriness

O-032

Hepatocyte-Specific MRI-Based Assessment of Indeterminate Hepatic Nodules in the Liver Transplant Evaluation of Cirrhotic Patients

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Aims: We aimed to determine the identities in explants of indeterminate hepatic nodules (IDNs) that had been scanned by dynamic magnetic resonance imaging (MRI), in order to establish clinico-radiological parameters predicting which IDNs are hepatocellular carcinomas (HCCs).

Methods: This study included 88 cirrhotic patients who underwent gadoxetic acid-enhanced MRI in pre-LT workup followed

within 90 days by primary liver transplantation (LT), in the Asan Medical Center. The MRI detected 168 hepatic nodules that were classified into 6 benign tumors, 49 HCCs, and 113 IDNs, in 5, 34, and 71 patients, respectively. We compared these pre-LT radiologic diagnoses and stagings with explant pathology on a per-lesion basis, to enable us to identify features of IDNs related to malignancy.

Results: Of the 168 nodules seen on MRI, 119 that were classified radiologically as consisting of 1 benign nodule (33.3%), 46 HCCs (93.9%), and 72 IDNs (63.7%) all turned out to be pathologic HCCs. Of 86 Milan-in patients staged by MRI, 11 progressed beyond the criteria after LT. HCC recurrence within 5 years of LT was most frequent in these recipients. High serum alpha-fetoprotein level (≥20 ng/mL) was the only per-patient factor significantly associated with malignant IDNs (Odds ratio [OR] 5.133, *P*=0.004). Per-tumor analysis of MRI signals revealed that arterial hyperintensity (OR, 3.45), hepatobiliary hypointensity (OR, 2.77), T2-weighted mild-to-moderate intensity (OR, 2.51), and restricted diffusion-weighted image (OR, 2.62) were significantly correlated with malignant IDN (ps<0.05). A model combining these 4 MRI factors and alpha-fetoprotein had the best performance for predicting the diagnosis of IDNs as HCCs in explanted livers.

Conclusions: Over 60% of the IDNs seen on dynamic images of cirrhotic livers proved to be HCCs when explanted livers were examined. It may be possible to identify HCCs with reasonable accuracy by means of their hepatocyte-specific MRI features in assessing patients for LT.

Keywords: Hepatocyte-specific MRI, Indeterminate hepatic nodules, Liver transplantation

O-033

Response to Sorafenib in Patients with Advanced Hepatocellular Carcinoma: Predictive Analytics Using Machine Learning with a Neighborhood-Group Detection Method

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Aims: Global guidelines indicate that sorafenib is the treatment of choice for patients with advanced hepatocellular carcinoma (HCC). However, only a few clinical markers have been suggested as predictors of the response to sorafenib. Owing to the nonlinear distribution characteristics of clinical variables, it is difficult to identify predictors by using conventional statistical analysis. To address this nonlinearity, we developed a neighborhood-group (N-group) detection method and investigated the predictors of the response to sorafenib treatment.

Methods: A previous cohort of patients that had been subjected to conventional statistical analysis (Lee M, et al. ILCA 2018 p-101; n=709) was re-analyzed. The analyses comprised: (1) calculation of the distance between all patient pairs; (2) defining N-groups based on an appropriate threshold distance and the minimum number of patients that should be included in the group; and (3) survival analysis of all N-groups. Subsequently, the clinical features of the N-groups were examined in detail to reveal the predictors related to survival differences.

Results: In total, 139 N-groups with distinct clinical features were found. In the survival analyses for all 9591 pairs of N-groups, 661 pairs of nearby N-groups were found to have significant differences in overall survival. According to the clinical characteristics of each N-group pair, various factors associated with the differences in survival were observed. The presence of portal vein thrombosis (PVT) and the absence of hand-foot syndrome (HFS) were commonly associated with poor survival. In N-group pairs without significant differences in PVT and HFS, the presence of extrahepatic metastasis and non-viral etiology was consistently associated with poor survival.

Conclusions: Through the use of an N-group detection method, we were able to identify predictors of the response to sorafenib that were consistent with the conventional analysis and additional factors. This new analytical method will provide a novel perspective for clinical analysis.

Keywords: Hepatocellular carcinoma, Sorafenib, Neighborhood-group

O-034

A Multi-National, Multi-Institutional Study of Comparing an Efficacy of Stereotactic Body Radiation Therapy and Radiofrequency Ablation for Hepatocellular Carcinoma

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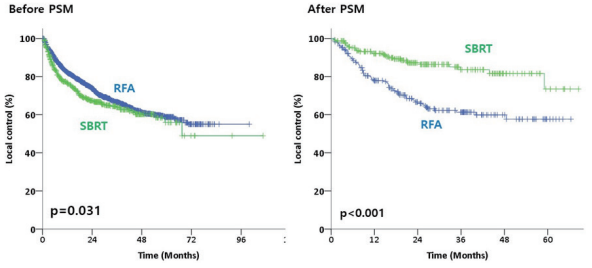
Aims: In the present study, we underwent a thorough analysis for comparing the effectiveness of SBRT to RFA in patients treated at 7 tertiary-referral hospitals.

Methods: Patients treated for HCC in 7 tertiary-referral hospitals were retrospectively reviewed. Among these, 1607 patients who underwent RFA of 1758 tumors and 505 patients who underwent SBRT of 519 tumors were included. Median prescribed total dose and fractional dose for SBRT were 48 (interquartile range, IQR, 40-54) Gy and 10 (IQR, 8-12) Gy, respectively. SBRT was delivered using CyberKnife (Accuray, Sunnyvale, CA) (n=158; 30.4%), Tomotherapy (Accuray, Madison, WI) (n=135; 26.0%), 3-dimensional conformal radiotherapy (n=112; 21.6%), and volumetric modulated arc therapy (Elekta, Stock-

holm, Sweden) (n=114; 22.0%). Patients were assessed after the completion of treatment at first month, every 3-6 months thereafter with CT or MRI, liver function tests, and tumor markers. Radiologic responses were evaluated using modified Response Evaluation Criteria in Solid Tumors to assess LC. Using propensity score matching (PSM) to adjust for clinical factors, 232 tumors were selected from each treatment arm.

Results: At baseline, SBRT-treated tumors were in more advanced BCLC stage (B-C, 64.3% vs. 15.7%, *P*<0.001), larger (median, 3.0 cm vs. 1.8 cm; *P*<0.001), and had a higher incidence of prior liver-directed treatments (median, 2 times vs. treatment naïve; *P*<0.001) than RFA-treated tumors. The median follow-up period for the entire cohort was 31.4 (IQR, 14.1-45.7) months. The 3-year LC rates were 63.9% for tumors treated with SBRT and 66.6% for tumors treated with RFA, respectively (*P*=0.031). In the univariate analysis for LC, tumor size, advanced stage (B or C), and serum AFP levels were attributed to local progression. However, treatment modality was significantly correlated with LC favoring SBRT (HR 0.74, 95% CI 0.59-0.92, *P*<0.001). Other independent factors included age, tumor size, advanced stage and serum AFP level in the multivariate analysis. After PSM, 3-year LC rates were 83.6% for tumors treated with SBRT and 61.3% for tumors treated with RFA, respectively (*P*<0.001). The Cox proportional hazards model in matched cohort also revealed that the treatment modality was significantly correlated with LC favoring SBRT (HR 0.29, 95% CI 0.18-0.45, *P*<0.001).

Conclusions: Although SBRT-treatment tumors had more negative prognostic factors at baseline, SBRT provided comparable LC rates to RFA in this multicenter retrospective analysis. Overall, SBRT was associated with a better LC rate than RFA in not only the entire cohort after adjusting clinical factors but also the matched cohort.



Keywords: Hepatocellular carcinoma, Radiofrequency ablation, Streotactic body radiation therapy

O-035

Practice Patterns, Radiologic Tumor Response, and Deterioration of Liver Function after Transarterial Chemoembolization (TACE): Final Analysis of OPTIMIS in Korea and Rest of Asia

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Aims: TACE is commonly used for patients (pts) with unresectable HCC (uHCC). However, there is no global consensus on TACE use.

Methods: OPTIMIS is an international, prospective, non-interventional study of uHCC pts for whom the decision to treat with TACE was made prior to enrollment. We report practice patterns, radiologic tumor response, liver deterioration, and subsequent treatments from Korea and rest of Asia. TACE ineligibility was analyzed per study protocol-specified criteria.

Results: Globally, 1,650 enrolled pts received TACE, including 292 from Korea and 459 from rest of Asia. Of those, 85/292 pts (29%) in Korea and 193/459 (42%) in rest of Asia were TACE ineligible at inclusion (Table). Excluding pts with prior sorafenib use, 109/292 (37%) in Korea and 100/459 (22%) in rest of Asia became TACE ineligible during the study. Of those, 6/109 pts (6%) in Korea and 3/100 (3%) in rest of Asia received sorafenib immediately after TACE ineligibility. In TACE administered pts, complete and partial response rates to first TACE were 24% and 36% versus 8% and 20% in Korea and rest of Asia, respectively. In pts with available laboratory values, chronic liver function deterioration (worsening in CTCAE grade 31–90 days post TACE) after first TACE was noted in Korea and rest of Asia: bilirubin (12% and 25%), albumin (22% and 24%), ALT (4% and 27%), and AST (9% and 31%).

Table. Disease characteristics and TACE ineligibility at inclusion in Korea and rest of Asia

(%)	Korea (n=292)	Rest of Asia (n=459)
Disease status		
EHS	25 (9)	33 (7)
PVT	30 (10)	22 (5)
BCLC stage		
B	204 (70)	284 (62)
C	79 (27)	154 (34)
D	3 (1)	10 (2)
Missing	6 (2)	11 (2)
Ineligible for TACE per study protocol-specified criteria	85 (29)	193 (42)

BCLC, Barcelona Clinic Liver Cancer; EHS, extrahepatic spread; PVT, portal vein thrombosis; TACE, transarterial chemoembolization.

Conclusions: TACE ineligibility criteria appear to be followed to a lesser extent in the rest of Asia compared with Korea. After the first TACE, liver function deterioration was noted in the chronic period and was higher in rest of Asia compared to Korea. In addition, radiologic tumor response rates were lower in rest of Asia compared to Korea. Our data highlight the need for evaluating TACE practice in uHCC to ensure pt eligibility for subsequent effective therapies.

Clinical Trial: NCT01933945

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Practice patterns, Tumor response, Liver function

O-036

Distinct Mutational and Molecular Patterns Associated with Family History in Hepatocellular Carcinoma

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Aims: Familial clustering is a common feature of hepatocellular carcinoma (HCC) as well as a risk factor for the disease. We sought to identify differences in the gene mutations and molecular alterations in patients with HCC who had a family history of the same disease versus sporadic cases.

Methods: Large genomic datasets of HCC [combined sets using whole exome sequencing and RNA-seq at Asan Medical Center (n=231) and TCGA LIHC dataset (n=316)] were analyzed to define distinct driver mutations, copy number variations, and diverse gene expressions based on the status of family history.

Results: Overall, approximately 27.3% of patients (160 out of 547) had a family history of HCC. A family history of HCC was predominantly more in female, white race, and older patients, and less in hepatitis B patients (Ps<0.05). Although the number of mutations was comparable between the two sets of tumors, the familial tumors contained different somatic mutation patterns with a greater frequency of alterations in TSC1, MYO18A, CNTN2, CLTCL1, SYNPO2, and DSCAM; and highly exclusive alterations in RPH3A, ERG, RNF146, PRKCZ, LMTK3, and FAM46D. Copy number alteration analysis disclosed distinguishable deletions in the 4q23 and 6q27 chromosome arm in the familial cases. In terms of mutational signature, signature 12 was more frequently exhibited signature 12 in HCC with family history, while signature 16 and 22 were less found. Differentially expressed transcripts in a subset of 516 tumors were significantly enriched in cellular metabolic process, especially, in pyruvate metabolism and the citric acid cycle pathway.

Conclusions: By multi-platform genomic profiling of HCC, we have refined our understanding of genetics events in familial HCC and identified clinical relevant alterations. This pathobiologic insight may serve as a fundamental backbone for precision prevention and treatment of HCC in actual practice.

Keywords: Hepatocellular carcinoma, Genomics, Family history, Mutation

7. Surgery,Biliary

O-037

Management of Pancreaticojejunostomy Stricture after Pancreaticoduodenectomy

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Aims: To explore the clinical management of pancreaticojejunostomy stricture (PJS) after pancreaticoduodenectomy (PD).

Methods: From July 2013 to Dec 2018, 17 patients with PJS were treated in our single center, including 10 male and 7 female, the average age was 61.3 years (49.1-73.8). All these patients had recurrent abdominal pain and acute pancreatitis. Among them, 7 were pancreatic cancer, 6 IPMN, 3 chronic pancreatitis and 1 periampullary carcinoma. The median time between PD to PJS was 38.1 months.

Results: 11 patients were successfully treated by Endoscopic dilation plus pancreatic drainage or EUS-guided rendezvous technique. Other 6 patients who failed the endoscopic technique, pancreaticojejunostomy (PJ) reconstruction was performed for 2 cases, PJ resected followed by pancreaticogastrostomy (PG) for 3 cases, and longitudinal PJ for 1 case. None of them had severe complication.

Conclusions: PJS is a late complication of PD that was less studied, the incidence is increasing since the survival time after PD was prolonged. Endoscopic treatment is our first choice. If the endoscopic technique failed, surgical treatment remains the only option. Commonly there are 4 kinds of surgical methods could be selected. PJ reconstructed, PJ resected followed by PG, Longitudinal PJ for 1 case. And posterior direct PG.

O-038

A Inverted Mattress Technique of Pancreaticojejunostomy for Laparoscopic Pancreatoduodenectomy

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Aims: Laparoscopic pancreatoduodenectomy (LPD) is a challenging abdominal operation requiring complex dissection and difficult reconstruction. Especially, pancreaticojejunostomy (PJ) reconstruction is considered the "Achilles heel" of LPD because pancreatic fluid leakage from the procedure is potentially significant morbidity. In the present report, we describe our experience with our inverted mattress (IM) method for LPD.
Methods: Between May 2016 and December 2018, a total of 143 patients with periampullary disease underwent PD at Kyungpook national university chilgok hospital. 43 patients underwent and Open PD was performed on 100 patients. The pancreatic stump was reconstructed using an our IM-PJ technique. Data on the demographic characteristics, operative outcomes and postoperative results of the cases were retrospectively collected and analyzed.
Results: Forty three patients received LPD and 7 patient was converted to open method. The mean age was 63.0 ± 12.0 years and gender ratio was 1:1. Mean ASA score and BMI were 1.8 ± 0.4 and 23.1 ± 3.4 respectively. The mean operation timewas 430 ± 73.2 min. Average blood loss was 107.8±194ml. Postoperative pancreatic fistula (POPF) of Grade B occurred in 5.6% and Grade C was not occurred. Also, delayed gastric emptying (DGE) occurred in 15.8%. The mean length of hospital stay was 12.4 ± 2.7 days and no postoperative mortality occurred.
Conclusions: The results of the present study suggest the a IM-PJ method is a safe for LPD that is associated with a low risk of POPF. However, these results should be verified by performing randomized control trials.

O-039

New Onset Diabetes and Reduction of Pancreatic Volume in Laparoscopic versus and Open Pancreaticoduodenectomy

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Aims: Atrophy of the remnant pancreas might be a risk factor for new onset diabetes mellitus (DM) after pancreaticoduodenectomy (PD). There was no comparative study of laparoscopic and open PD for differences in change of remnant pancreatic volume and incidence of new onset DM after surgery.
Methods: Fifty-seven patients underwent laparoscopic PD and 43 patients underwent open PD for periampullary pathologies between March 2014 and September 2018 were included. All patients underwent duct-to-mucosa pancreaticojejunostomy for the reconstruction of the remnant pancreas. The perioperative outcomes including the incidence of new onset DM were examined. The pancreatic volume was measured 1 week and 3 months after surgery using computer tomography volumetry.
Results: The mean age, ratio of sex, and mean body mass index of patients were comparable between the two groups. The operative time was comparable (417 ± 83 vs. 392 ± 87 min, *P*=0.638), but the estimated blood loss was lesser in laparoscopic group (402 ± 391 vs. 945 ± 402 ml, *P*=0.002). Postoperative complications greater than grade II were not difference (5 vs. 5 cases, *P*=0.659). Incidence of new onset pancreatogenic DM was not different (7 vs. 6 cases, *P*=1.000). The pancreatic volume reduction rate 3 months after PD was similar in both laparoscopic and open PD (11.1 ± 17.2 vs. 10.1 ± 12.3 ml, *P*=0.749).
Conclusions: This study suggests that the laparoscopic PD with duct-to-mucosa pancreaticojejunostomy was safe and did not deteriorate the atrophic changes of the remnant pancreas and development of new onset DM.

O-040

Preoperative Serum Glucose to Lymphocyte Ratio as an Independent Prognostic Factor: Developing 3-Scored Survival Estimating System in Resected Pancreatic Ductal Adenocarcinoma

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Aims: We hypothesized that elevated glucose to lymphocyte ratio (GLR) might be a sensitive prognostic biomarker to determine the disease specific survival of pancreas ductal adenocarcinoma (PDAC). Moreover, we try to develop scoring system to predict the prognosis of PDAC by using only clinically available preoperative parameters.
Methods: Between May 1999 and August 2016, 244 patients with resectable PDAC underwent surgical resection at Severance Hospital, Korea. Medical records were retrospectively reviewed. The preoperative clinical parameters, inflammatory markers, glucose, GLR, albumin, tumor size, carbohydrate antigen (CA) 19-9, and follow up data were collected. Survival analysis and Cox regression were performed to evaluate oncologic outcomes.
Results: Among the preoperative detectable parameters, 1) GLR >105.5 (HR=1.6074, 95% CI: 1.119-2.308 *P*=0.0102), 2) CA19-9≥150 (HR=1.432, 95% CI: 0.999-2.053, *P*=0.0405), and 3) tumor size ≥2 cm (HR=1.586, 95% CI: 1.113-2.259, *P*=0.0106) were independent prognostic factor in determining long-term cancer-specific survival by multivariate analysis. We developed 3-scored survival estimating system (0 to 3) by summing these three parameters. Overall survival is significantly different according to clinically divided subgroups by 3-scored survival estimating system (*P*<0.001).
Conclusions: GLR is an independent prognostic factor of disease-specific survival in PDAC. Based on preoperative detectable parameters including GLR, CA 19-9, tumor size, we developed 3-scored survival estimating system which can serve as a model for assessing the possibilities of individual treatment option for PDAC patients.

O-041

Development and Validation of a Novel Topical Agent for Gallstone Dissolution

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Aims: Although MTBE is the only clinical topical agent for gallstone dissolution, its use is limited by its side effects mostly arising from a relatively low boiling point (55 ℃).
Methods: The dissolubility of MTBE and MMP *in vitro* was determined by placing human gallstones in glass containers with either solvent and, then, measuring their dry weights. Their dissolubility *in vivo* was determined by comparing the weights of solvent-treated gallstones and control (dimethyl sulfoxide)-treated gallstones, after directly injecting each solvent into the gallbladder in hamster models with cholesterol and pigmented gallstones.
Results: In the *in vitro* dissolution test, MMP demonstrated statistically higher dissolubility than did MTBE for cholesterol and pigmented gallstones (88.2% vs. 65.7%, 50.8% vs. 29.0%, respectively; $P<0.05$). In the *in vivo* experiments, MMP exhibited 59.0% and 54.3% dissolubility for cholesterol and pigmented gallstones, respectively, which were significantly higher than those of MTBE (50.0% and 32.0%, respectively; $P<0.05$). The immunohistochemical stains of gallbladder specimens obtained from the MMP-treated hamsters demonstrated that MMP did not significantly increase the expression of cleaved caspase 9 or significantly decrease the expression of proliferation cell nuclear antigen.
Conclusions: This study demonstrated that MMP has better potential than does MTBE in dissolving gallstones, especially pigmented gallstones, while resulting in lesser toxicities.

O-042

Robotic Surgery for Gall Bladder Cancer: Operative Technique and Early Outcomes

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Aims: The objective of this study was to compare the early outcomes of robotic radical cholecystectomy (RRC) with open radical cholecystectomy (ORC) for gall bladder cancer (GBC).
Methods: Patients who underwent RRC for suspected or incidental GBC between July 2015 to August 2018 were analysed. Patients who underwent ORC during the same period and fulfilled the study criteria formed the control group.
Results: During the study period, 27 patients who underwent RRC formed the study group (Group A) and 70 matched patients who underwent ORC formed the control group (Group B). Median surgical time was higher in Group A (295 versus 200 mins, $P<0.001$). However, median blood loss (ml) (200 versus 600 ml, $P<0.001$), postoperative hospital-stay (4 versus 5 days, $P=0.046$) and postoperative morbidity (1 versus 15 patients, $P=0.035$) were lower in Group A. Median lymph node yield was 10 (range=2-21) for Group A and 9 (range=2-25) for Group B, and was comparable ($P=0.408$). During a median follow up of 9 (1-46) months, 2 patients in Group A (no port site recurrence) and 12 patients in Group B developed recurrence.
Conclusions: RRC is safe and feasible and the short-term results are comparable to ORC.

O-043

Laparoscopic Pancreaticoduodenectomy: CUSUM Analysis in a Developing Single Surgeon

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Aims: Laparoscopic pancreaticoduodenectomy (LPD) was the one of most technically challenging operations of minimally invasive surgery (MIS). This retrospective study aimed to analyze the learning curve of a single surgeon who carried out 63 LPD in a single center.
Methods: From August 2015 to August 2018, 63 patient underwent laparoscopic pancreaticoduodenectomy in hallym sacred heart hospital by a single surgeon. The patient characteristics, perioperative variables, and immediate postoperative outcomes were retrospectively collected and analysed. The cumulative sum (CUSUM) analysis was used to identify the inflexion points which corresponded to the learning curve.
Results: From the CUSUM analysis, two distinct phase of the learning curve were identified (early group:1-34 cases and late group: 35-63 cases). Among two groups, there was no significant difference in perioperative oucomes. Non-significant reduction were observed in operation time (mean, 448 min vs. 425 min, $P=0.239$), conversion rate (8.8% vs. 3.4%, $P=0.618$), postoperative complication (Clavien-Dindo grade III or higher, 26.5% vs. 20.7%, $P=0.768$), and intraoperative transfusion rate (35.3% vs. 20.7%, $P=0.267$). Except pancreas adenocarcinoma, two distinct phase of the learning curve were identified (early group: 1-31 cases and late group: 32-45 cases). there was significant difference in operation time(mean, 439 min vs. 367 min, $P<0.001$) and intraoperative transfusion rate (35.5% vs. 7.1%, $P=0.07$). Non-significant reduction were observed in conversion rate, postoperative stay, and complication.
Conclusions: Laparoscopic pancreaticoduodenectomy can be safely and feasibly performed selected cases by experienced hepatobiliary-pancreas surgeons. Conservatively, the learning curve was completed after about 30 LPD in excluding PDAC.

O-044

Upfront vs. Delayed Laparoscopic Assisted Necrosectomy for Infected Pancreatic Necrosis

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Aims: To delay the surgery, percutaneous or endoscopic drainage was usually performed as the first step in step-up approach for infected pancreatic necrosis (IPN). However, drainage was unnecessary or unavailable in some patients. To explore the safety and effect of upfront laparoscopic assisted necrosectomy in treatment of IPN.

Methods: IPN patients received surgical therapy in our center between January 2015 and December 2017 were included in this study. Patients were assigned to either single or step-up group according to the received therapeutic approach. Incidence of complications, death, total number of surgical intervention and total hospital stay were compared. Logistic regression and nomogram were used to explore the risk factors and probability for patients undergoing surgical intervention ≥3 times.

Results: There were 45 and 49 patients included in single step and step-up group, respectively. No significant difference between groups in terms of new organ failure (14.29% vs. 14.33%, *P*=0.832), death (8.89% vs.8.17%, *P*=0.949) and long-term complications (18.37% vs. 15.56%, *P*=0.717). However, the number of surgical intervention in single step group was significant less than in step-up group with shorter hospital stay. After multivariate analysis, CRP, IL-6 and surgical approach were independent predicators for patients undergoing surgical intervention ≥3. A nomogram was built with area under ROC curve 0.891.

Conclusions: Compared with step-up approach, single up surgery was safe and effective in selected IPN patients with less number of surgical intervention and shorter hospital stay.

8. Surgery,Technical Issues

O-045

Parietal Peritoneum as an Autologous Substitute for Middle Hepatic Vein Reconstruction during Living-Donor Liver Transplantation

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Aims: Draining the anterior section of the graft liver prevents congestion and preserves the graft function when using right lobe for living-donor liver transplantation (LDLT). Autologous, cryopreserved, or artificial vascular graft can be used as an interpositional vascular substitute. However, they are not always available, time-consuming, expensive, or associated with a risk of infection. The parietal peritoneum can be a good alternative to solve these problems. This study reports the first 16 cases of LDLT using parietal peritoneum for middle hepatic vein reconstruction.

Methods: Between May 2016 and February 2019, 16 patients underwent LDLT using right lobe with reconstruction of middle hepatic vein using the patients' own parietal peritoneum. This study was reviewed and approved by the institutional review board of the author's institution.

Results: V5 was reconstructed in 16 patients and V8 in 11 patients. The mean hospital stay was 17.4 days. The 7-days and 32-days patency rates were 56.3% and 37.5%. All patients survived with tolerable liver function tests. There were 2 patients who experienced early major complication; one experienced middle hepatic vein thrombosis which required aspiration thrombectomy and stent insertion and the other one experienced bile duct leakage which required endoscopic biliary drainage. There were 3 patients experienced late major complication including one portal vein stenosis, one bile duct stricture, and the other one bile leakage. There was no infection related complication. After initial experience, all of the recent 6 cases showed good patency until discharge and are under follow up.

Conclusions: Parietal peritoneum can be safely used as an autologous substitute for middle hepatic vein reconstruction during LDLT.

Keywords: Peritoneum, Living donor liver transplantation, Graft, Middle hepatic vein

O-046

Prospective Multicenter Study for Robotic Anatomic Major Liver Resection

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Aims: Robotic surgical system had been widely accepted in various surgical field with the expectations of overcoming the limitation of laparoscopic surgery. However, robotic liver resection had not generalized, so far. Thus, this study aimed to evaluate the feasibility and safety of robotic major liver resection by prospective multicenter study.

Methods: From July 2017 to December 2018, five surgeons who were novice in robotic liver resection but experienced a lot in open and laparoscopic liver resection in five tertiary hospitals performed 46 cases of robotic major anatomical liver resection. Perioperative patient's clinical data and surgical data were prospectively collect-

ed. All operations were performed identical procedures for dissection and hemostasis and were totally robotic approach.
Results: 22 cases of left hemihepatectomy, 1 case of extended left hemihepatectomy, 14 cases of right hemihepatectomy, 2 cases of right anterior sectionectomy, 6 cases of right posterior sectionectomy, and one cases of central bisectionectomy were performed. Total operation time was 378.58 ± 124.31 (190~696) minutes and estimated intraoperative blood loss was 276.67 ± 397.41 mL (minimal ~ 2600mL). Overall complications were developed in 16 cases (34/8%). In terms of severe surgical complications, there were 3 cases of postoperative fluid collection treated with drainage and one case of bile leakage treated with percutaneous trans-hepatic biliary drainage. Only one case out of 46 cases was converted to the conventional open left hemihepatectomy by bleeding.
Conclusions: In this study, robotic anatomic major liver resection might be safely performed even by robotic beginners but advanced open and laparoscopic liver surgeons.

O-047

Selective Occlusion of the Hepatic Artery and Portal Vein Improves Liver Hypertrophy for Staged Hepatectomy

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Aims: To evaluate the safety and feasibility of a new method of selective occlusion of the hepatic artery and portal vein (SOAP) for staged hepatectomy (SOAPS) in patients with hepatocellular carcinoma (HCC).
Methods: Ten patients with unresectable HCC due to insufficient volume of future liver remnant (FLR) were chosen to undergo SOAPS. SOAP without liver partition was performed in the first stage of hepatectomy. The second stage of hepatectomy, including right hemihepatectomy, right trisectionectomy and left trisectionectomy, was performed when the FLR was sufficient.
Results: None of the patients developed hepatic failure and no deaths occurred following SOAP. The FLR in all patients increased by an average of 144.3 mL after SOAP.The average ratio of FLR to standard liver volume increased from 32.6% to 44.7%. The second stage of hepatectomy was performed 8 to 18 days after SOAP. The average time interval between the two stages was 14.4 days. No in-hospital deaths occurred after SOAPS. The AFP level in 8 patients reduced to normal within two months after SOAPS. Of these 10 patients, 4 patients died of intrahepatic recurrence, lung metastasis or bone metastasis. Six survived to now, and the longest survival time is 40.2 months. Of the 6 surviving cases, 4 patients are without disease.
Conclusions: SOAP can facilitate rapid and sustained FLR hypertrophy. In addition to reported portal vein blood redistribution, hepatic artery blood redistribution is one of the mechanisms of liver hypertrophy in SOAP. SOAPS is safe and effective in patients with unresectable HCC.

O-048

The Anatomical Characteristics of Patients with Posterior Bile Duct Stricture after a Liver Resection Including Anterior Section

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Aims: When deciding to proceed with anterior sectionectomy or central bisectionectomy, the posterior duct anatomy must be carefully reviewed due to the high variation rate and the risk of biliary complication.
Methods: We reviewed the clinical data of patients who received liver resections including the anterior section such as anterior sectionectomy and central bisectionectomy from July of 2009 to September of 2018. We investigated the type of bile duct anatomy and the right hepatic duct length was measured if the classification was type A. We excluded patients without MRI and patients who underwent hepaticojejunostomy. We divided patients into 4 groups according to the bile duct anatomy and risk factor analysis for right posterior bile duct stricture.
Results: A total of 69 patients received central bisectionectomy or anterior sectionectomy. The type A bile duct was most common (n=42, 60.9%) and type B was the second most type (n=12, 17.4%). Five patient (7.2%) need PTBD or ERCP procedures due to biliary stricture and occurs in only type A. The length of right hepatic duct (RHD) was related to biliary stricture (AUC=0.889) and the sensitivity was 0.8 and specificity was 0.889 when the length of RHD is 12 mm. In multivariate analysis, the RHD more than 12 mm was significant (OR: 47.068, 1.469 – 1508, *P*=0.029). The median time to biliary stricture was postoperative 34 day (5-81) and the stricture was managed with ENBD and PTBD and successfully resolved.
Conclusions: The RHD more than 12 mm was the risk factor of the posterior biliary stricture in anterior or central bisectionectomy.

O-049

Clinical Outcomes of Laparoscopic Living Donor Right Hepatectomy without Pringle's and Hanging Maneuver

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Aims: Careful preparation and blood-saving surgery will significantly lower the postoperative morbidity in laparoscopic liver resection (LLR). To reduce bleeding during hepatectomy, it is

significant to decrease central venous pressure (CVP) and apply Pringle's & hanging maneuver (P&H). However, P&H are cumbersome and has the potential for further injury by excessive mobilization and dissection of inferior vena cava and right lobe of liver, especially in living liver donors. We would like to present the experience and outcomes of laparoscopic living donor right hepatectomy (LDRH) performed without P&H.

Methods: Between December 2014 and October 2018, among 97 cases of living donor right hepatectomy, 50 donors underwent LDRH. During LDRH, mean pneumoperitoneal pressure was 12 mmHg and CVP was less than 5 mmHg. The right liver was mobilized to the inferior half portion of retrohepatic IVC and large right inferior hepatic veins were preserved. The caudal approach without P&H was applied for liver parenchymal transection. The V5 and V8 for reconstruction were also preserved until just before the right hepatic duct transection.

Results: Mean total operation time was 367 minutes and the warm ischemic time was 9.2 minutes. No donors required blood transfusion, conversion to open surgery, and re-operation. The postoperative course was uneventful. All donors' liver function was recovered to normal range within 2 weeks and mean postoperative hospital stay was 8 days.

Conclusions: Conclusively, LLR under low CVP and constant pneumoperitoneal pressure without P&H can help reduce blood loss and prevent further liver graft injury by excessive mobilization of liver.

O-050

Right and Ventral Margins of Paracaval Portion of Caudate Lobe: Studies from Cadaveric Dissection and 3D Reconstruction Analysis Using Synapse 3D Software

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Aims: As the hilar cholangiocarcinoma holds the possibility of metastasis via minute bile duct branches to caudate lobe, total caudate lobectomy along with hepatic resection is necessary. This study was designed to figure out the utility of using Synapse 3D in the right and ventral margins of caudate lobe before caudate lobectomy.

Methods: 18 cadaveric liver specimens were dissected and by calculating the distance from the right side of inferior vena cava (IVC) and height from the hilar plate of a rightmost branch, we figured out the right margin and ventral margin of paracaval portion, respectively. 39 preoperative liver computed tomography images were obtained from donors and reconstructed by Synapse 3D software.

Results: In the respect of right margin, the mean length in Synapse 3D group was 1.7 cm, greater than 1.2 cm of cadaveric dissection group meaningfully (P<0.05). Synapse 3D showed 4 types of ventral margin. Type 1: the ventral margin of paracaval portion is restricted to the dome-like area between the middle hepatic vein (MHV) and right hepatic vein (RHV) insertion to the IVC (30 cases, 76.9%); Type 2: ventral margin extends beyond this dome-like area (7 cases, 17.9%); Type 3: ventral margin extends beyond the RHV (1 case, 2.6%); Type 4: ventral margin extends beyond both RHV and MHV-RHV dome-like area (1 case, 2.6%).

Conclusions: The image of the right margin and ventral margin of the paracaval portion can be reconstructed and measured by Synapse 3D, we think it is beneficial for more precise caudate lobectomy clinically.

O-051

Short Term Result of Parenchymal Sparing Anatomical Liver Resection Based on Portal Ramification of the Right Anterior Section: A Single Center Experience

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Aims: Anatomical liver resection is the treatment of choice for hepatocellular carcinoma (HCC). However, the remnant liver volume is equally important in patient selection for operation. Recent appreciation of the liver segmentation divided the right anterior section (RAS) into segment 5-segment 8 or ventral-dorsal segment. Thus, we aim to evaluate the short term results of parenchymal sparing liver resection based on portal ramification of the right anterior section.

Methods: From July 1 to December 30, 2018, 12 patients with HCC underwent parenchymal sparing right hepatectomy. The portal ramification of RAS were analyzed using the Multidetector Computed Tomography scan. The procedures were performed by 4 liver surgeons.

Results: Among 12 patients, there were 10 men and 2 women. The mean age was 60.6 ± 6.9 years. The right hepatectomy with segment 8 parenchymal sparing was performed in 1 patient with cranio-caudal type of the RAS. In 11 patients with ventro-dorsal type, we performed 10 ventral-segment preserving right hemihepatectomy and 1 dorsal preserving mesohepatectomy. The mean operative time was 262.5 ± 40.1 minutes with a mean estimated blood loss of 404.2 ± 362.4 ml. One liver failure was reported (Clavien-Dindo classification, grade 2). The mean length of hospital stay was 10.9 ± 3.9 days. There was no reported 30 days mortality.

Conclusions: The pre-operative evaluation of RAS's anatomy is very important to decide the method of parenchymal sparing

liver resection. This procedure is technically safe and feasible.

O-052

Improved Outcomes of Laparoscopic Liver Resection for Hepatocellular Carcinoma Located in Posterosuperior Segments of the Liver

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Aims: Laparoscopic liver resection (LLR) is widely adapted for hepatocellular carcinoma (HCC), while LLR in posterosuperior (PS) segments is still challenging. However, with recent improvement of techniques and accumulation of experiences, LLR in PS segments is feasible. We compared outcomes of LLR for HCC located in PS segments before and after the adaptation of technological improvements.

Methods: We retrospectively analyzed 149 patients who underwent LLR for HCC located in PS segments from September 2003 to December 2016. The patients were divided into group 1 (n=43) and group 2 (n=106) who underwent LLR before and after 2012, when advanced techniques including use of intercostal trocars, Pringle maneuver, and semi-lateral position of patient were adapted. We also compared these patients with those who underwent open liver resection (OLR; n=124) for HCC in PS segments at the same period.

Results: Mean operative time (395 minutes vs 331 minutes; *P*=0.013), intraoperative blood loss (1545 ml vs 1219 ml; *P*=0.020), and hospital stay (12 days vs 9, *P*<0.001) were significantly less in group 2. Postoperative complication rate (18.6% vs 18.9%; *P*=0.970), open conversion rate (23% vs 17%; *P*=0.374), 5-year overall survival (79% vs 89%; *P*=0.607) and 5-year disease free survival (52% vs 53%; *P*=0.657) rates were not significantly different between the groups. The proportion of LLR increased (36% vs 69%, *P*<0.001). Compared to OLR group, complication rate (40.3% vs 18.8%; *P*<0.001) and hospital stay (18 days vs 10 days; *P*<0.001) were significantly lower in LLR group.

Conclusions: The complexity of LLR for HCC in PS segments has been gradually overcoming by the adaptation of advanced techniques.

Keywords: Hepatectomy, Complication, Survival, Prognosis

9. ALD & NAFLD

O-053

Combinatorial Effect of Ezetimibe and Empagliflozin on NAFLD in Choline Deficient High Fat Diet-Induced Murine Model

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Aims: Sodium-glucose cotransporter 2 inhibitor (SGLT2i) and ezetimibe, a cholesterol-lowering drug by targeting NPC1L1, have shown therapeutic potential for non-alcoholic fatty liver disease (NAFLD). As SGLT2i and ezetimibe have different pharmacological mechanisms, we hypothesized that the combination of empagliflozin (selective SGLT2i) and ezetimibe could improve NAFLD additively.

Methods: We used the choline-deficient high fat diet (CD-HFD)-induced murine model of NAFLD that has key features of human metabolic syndrome. 6 week-old C57BL/6J mice were fed with CD-HFD for 8 weeks. Then these mice were divided into four groups: vehicle, ezetimibe (10 mg/kg), empagliflozin (10 mg/kg), and ezetimibe (10 mg/kg) + empagliflozin (10 mg/kg). After 8 weeks, mice were sacrificed and subjected to blood measurements, and tissues for RNA isolation, lipid measurements and histology.

Results: CD-HFD-fed mice group exhibited liver weight gain with lipid accumulation and increased serum alanine aminotransferase (ALT). Ezetimibe, empagliflozin, and combination therapy significantly reduced liver steatosis. However, the histological NAFLD activity score (NAS) was most improved in the ezetimibe/empagliflozin group (0.667) than in the ezetimibe group (2.0, *P*=0.032) or empagliflozin group (2.33, *P*=0.043). Hepatic lipid contents were also significantly lower in the ezetimibe/empagloflozin group compared to other groups. In the insulin tolerance test, glucose level was most reacted in ezetimibe/empagliflozin group. Hepatic expression of lipogenesis genes such as Acc1 (Acetyl-CoA carboxylase 1) and Fas (fatty acid synthase) were significantly decreased in the ezetimibe/empagliflozin group. But hepatic expression of ß-oxidation-related genes or esterification genes were not significantly decreased in the ezetimibe/empagliflozin group.

Conclusions: These findings suggested combined administration of empagliflozin and ezetimibe can additively improve NAFLD through decreasing lipogenesis process.

Keywords: NAFLD, CD-HFD, Ezetimibe, Sodium-glucose co-transporter 2, Combination therapy

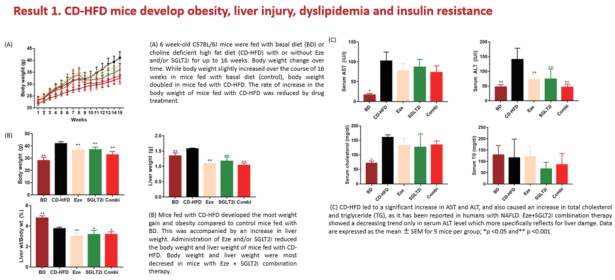

Figure 1.

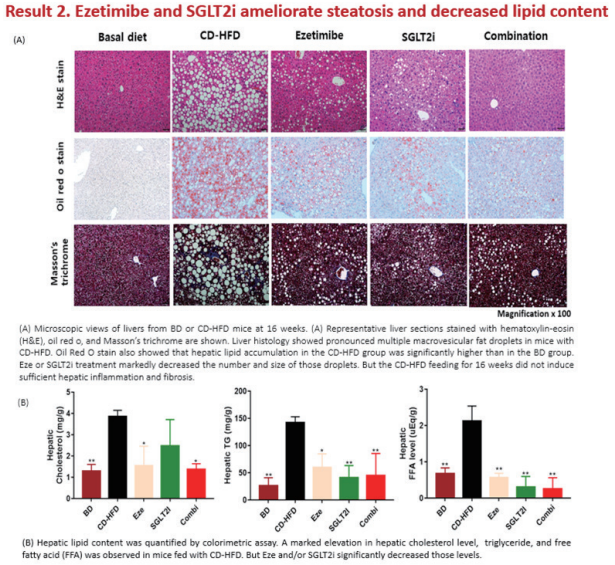

Figure 2.

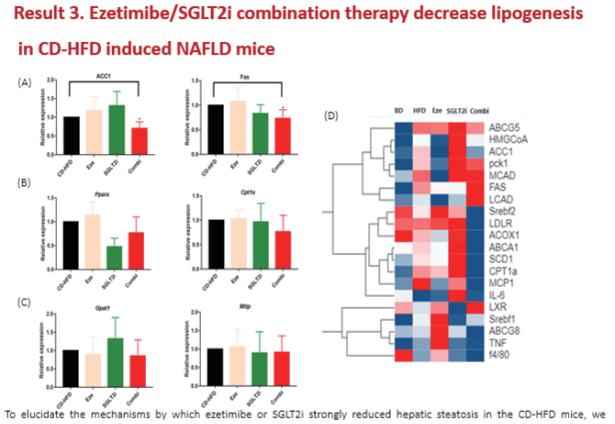

Figure 3.

O-054

Nicotinamide Riboside Does Not Attenuate Steatosis but Improve Inflammation in Non-Alcoholic Steatohepatitis Induced by Methionine-Choline Deficient Diet

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Aims: Mitochondria dysfunction is one of important pathophysiologic mechanisms in non-alcoholic fatty liver disease. Nicotinamide adenine dinucleotide (NAD^+) supplementation by nicotinamide riboside (NR) was reported to improve hepatocyte mitochondria function. We evaluate the efficacy of NR administration in non-alcoholic steatohepatitis (NASH) induced by methionine-choline deficient (MCD) diet in mice.

Methods: Mice were fed MCD diet or normal chow diet for 8 weeks. NR, a precursor of NAD^+ biosynthesis, was added either as a preventive strategy (NR-prevention group) or as a therapeutic intervention (NR-therapy group) in MCD diet group.

Results: MCD diet induced severe macrovesicular fat change and moderate periportal inflammation in mice. NAD^+ content in liver lysate and mitochondria decreased in MCD diet group and increased in both NR-prevention and NR-therapy groups (mitochondria NAD^+ [pmole/10^6 cells]; 3938.5, 1208.0, 3104.5, and 2503.0 in control, MCD diet, NR-prevention and NR-therapy group, respectively, P<0.001). NR administration also increases the hepatic ß-oxidation and mitochondrial complex content and activity (citrate synthase activity [fold change]; 1.00, 1.20, 1.70 and 2.20, in control, MCD diet, NR-prevention and NR-therapy group, respectively, P<0.001). Inflammatory transcripts (tumor necrosis factor-α, MCP-1, interleukin-1ß and interleukin-6) increased in MCD diet group and decreased with NR treatment (tumor necrosis factor-α relative mRNA expression; 1.01, 4.97, 1.58 and 1.28 in control, MCD diet, NR-prevention and NR-therapy group, respectively, P<0.001). However, histologic liver tissue sections did not showed the improvement of steatosis and only showed modest improvement of periportal inflammation in NR-prevention and NR-therapy group.

Conclusions: Hepatic NAD^+ repletion by NR administration does not attenuate steatosis but improve inflammation in NASH by MCD diet.

Keywords: Non-alcoholic fatty liver disease, Mitochondria, Nicotinamide adenine dinucleotide, Inflammation

O-055

PNPLA3 Genetic Polymorphisms Associated with the Development of Non Alcoholic Fatty Liver Disease in Korea Biobank Network

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Aims: The patatin-like phospholipase domain-containing protein-3 (PNPLA3) rs738409 genotype (major genetic variant associated with non-alcoholic fatty liver disease [NAFLD]) confers high cross-ethnicity risk for NAFLD and non-alcoholic steatohepatitis (NASH) development. This study aimed to investigate the correlation between gene polymorphism of *PNPLA3* and genetic susceptibility of NAFLD and NASH using the Korea Biobank Project (KBP) database.

Methods: Our study population comprises the city cohorts (n=3698) and rural cohorts (n=6030) of Korean Genome and Epidemiology Study provided by KBP. Genotype data of single nucleotide polymorphisms (SNPs) were retrieved by using Affy 6.0 and Illumina Exome Chip ver 1.1 of KBP network from January 2004 to December 2012. *PNPLA3* SNPs were assessed for the risk of NAFLD and NASH development by chi-square tests followed by logistic regression analyses. NAFLD was diagnosed when the individuals had a radiologic evidence of fatty liver, and had neither viral hepatitis nor history of alcohol drinking. Among the NAFLD patients, NASH was diagnosed if the patient had serum ALT > 50 IU/L.

Results: The total population (n=9,728) had a mean age of 56-year, and 26% were male gender. In terms of *PNPLA3* rs738409 genotypes, there were 628 (17%) *GG*, 1803 (49%) *GC*, and 1262 (34%) *CC* genotype in city cohorts, whereas there were 981 (16%) *GG*, 2968 (49%) *GC*, and 2081 (35%) *CC* genotype in rural cohorts. Radiologic exam data were available in 3698 subjects in city cohorts and 2236 subjects in rural cohorts. There were 61 (1.6%) NAFLD subjects in city cohorts (n=3698), and 59 (2.6%) NAFLD subjects in rural cohorts (n=2236). Among them, 12 (19%) subjects had NASH in city cohorts and 15 (25%) had NASH in rural cohorts.Age and sex matched case-control analysis could not be done because of the relatively low prevalence of NAFLD (1.6 ~ 2.6%) in our cohorts and a potential selection bias. In the unmatched case-control analyses, 61 NAFLD subjects and 1,658 healthy control subjects were enrolled in city cohorts, and 59 NAFLD and 1,089 healthy control subjects in rural cohorts. In univariate analysis, there was no significant association between the *PNPLA3* rs738409 genotypes and the development of NAFLD both in city cohorts and in rural cohorts (P>0.05), neither was between the NASH development and the *PNPLA3* rs738409 genotypes. Nevertheless, in logistic regression analysis with adjustment for age and sex, *PNPLA3* rs738409 *GG* genotype showed a tendency towards NAFLD development (Adjusted OR = 1.27, P=0.07) in the unmatched combined cohorts (n=2,867).

Conclusions: Using the city and rural cohorts of KBP database, no significant association was observed between the *PNPLA3* rs738409 genotypes and risk of NAFLD or NASH. Further studies with higher quality and larger population will be needed to obtain a more precise estimate of the genetic effects on NAFLD susceptibility including *PNPLA3*.

Keywords: Single nucleotide polymorphism, Korean, PNPLA3, Non-alcoholic fatty liver disease

O-056

Gut-Microbiome Taxonomic Profiling as Non-Invasive Biomarkers for the Early Detection in Alcoholic Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is a prevalent form of primary liver cancer and represents the fifth leading cause of worldwide cancer mortality. Though early diagnosis of HCC is important, so far lacks of effective biomarker for early diagnosis of HCC have been a problem. In this study, we searched for potential taxonomic biomarkers of HCC by using metagenomics approach.

Methods: Between September 2017 and April 2019, normal controls (n=16), alcoholic cirrhosis (n=24), and HCC (n=7) groups were prospectively enrolled and analyzed. 16S-based Microbiome Taxonomic Profiling (MTP) platform of EzBioCloud Apps (ChunLab Inc., Korea) was performed and comparative MTP analyzer of EzBioCloud Apps was used for comparative analysis of groups.

Results: At the phylum level, proportion of the Bacteroidetes in cirrhosis patients compared with normal patients has shown significant differences (P<0.05). In species richness, alpha diversities (410, 223 and 203) were different and decreased according to the ALD progression (normal control, cirrhosis and HCC, P<0.05). In taxonomic biomarker analysis at family level (normal control and HCC), *Prevotellaceae* (31.0 and 4.7), *Selenomonadaceae* (2.2 and 0.1), *Muribaculaceae* (1.2 and 0.1), *Christensenellaceae* (0.2 and 0.0) and *Ruminococcaceae* (8.5 and 2.9) were significantly different. At genus level, *Faecalibacterium, Prevotella, Oscillibacter, Proteus and Lachnospira* were significantly decreased (P<0.01) in HCC patients. In the analysis of taxonomic biomarker between cirrhosis and HCC, *Akkermansiaceae* (2.4 and 0.0), and *Christensenellaceae* (0.1 and 0.0) were decreased and *Hafniaceae* (0.0 and 0.1) was increased (P<0.05). *Akkermansia, Blautia, Megamonas, Clostridium*_g21, and *Leuconostoc* were significantly decreased (P<0.05) in HCC patients.

Conclusions: Our integrative approaches highlighted taxonomic differences among normal control, cirrhosis, and HCC and portends the early onset of HCC. Some microbiomes, including *Akkermansia,* can be used as a biomarker for the early detection of HCC.

Keywords: HCC, Gut microbiome, Microbial taxonomic profiling, Biomarkers

O-057

Serum MFG-E8 Level as a Potential Biomarker for the Evaluation and Prediction of the Metabolic Syndrome

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Aims: Diagnosis and prediction of metabolic syndrome (MS) is cumbersome and so MS often goes unnoticed. Thus, better biomarkers for earlier diagnosis are needed. Serum milk fat globule-EFG factor 8 protein (MFG-E8) is an inflammatory glycoprotein that mediates the clearance of apoptotic cells.

Methods: Serum samples of 556 subjects in the Korea University Metabolic syndrome cohort was analyzed.

Results: Age was 55.1±6.5 years and 277 subjects (49.8%) were men. Diabetes, hypertension, and MS was present in 103 (18.5%), 299 (53.8%), and 236 subjects (42.4%), respectively. Serum MFG-E8 level was significantly correlated with diastolic blood pressure (Pearson's correlation coefficient 0.146, *P*=0.001), mean arterial pressure (0.120, *P*=0.005), serum total cholesterol (0.121, *P*=0.005), high-density lipoprotein cholesterol (-0.160, *P*<0.001), triglyceride (0.618, *P*<0.001), glucose (0.213, *P*<0.001) levels and pulse wave velocity (0.134, *P*=0.002). The area under the receiver operating characteristic curve (AUROC) of serum MFG-E8 level for the prediction of MS was 0.644 (95% confidence interval [CI], 0.597-0.691; *P*<0.001), and the optimal cutoff value was 4745.1 pg/mL (sensitivity 41.9%, specificity 82.5%). In 320 subjects without MS at baseline, MS was developed in 122 subjects (38.1%), and serum MFG-E8 level was significantly higher in these patients than other subjects (4029.0±1321.9 pg/mL vs. 3636.4±1315.3 pg/mL, *P*=0.010). AUROC of serum MFG-E8 level for the prediction of development of MS in subjects without MS at baseline was 0.595 (95% CI, 0.532-0.658; *P*=0.004), and the optimal cutoff value was 3732.5 pg/mL (sensitivity 57.4%, specificity 58.6%). When subjects were classified according to the cutoff of 3732.5 pg/mL of serum MFG-E8 level, the prevalence of development of MS was significantly higher in subjects with serum MFG-E8 level >3732.5 pg/mL than in those with serum MFG-E8 level >3732.5 pg/mL (46.1% vs. 31.0%, *P*=0.005).

Conclusions: Serum MFG-E8 might be used as a biomarker for the diagnosis and screening those at risk of developing metabolic syndrome.

Keywords: Serum milk fat globule-EFG factor 8, Metabolic syndrome, Biomarker, Diagnosis

O-058

Long-Term Risk of a Nonalcoholic Fatty Liver after Tamoxifen Use in Breast Cancer: Propensity Score Matching Analysis

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Aims: Fatty liver has been known to be the common side effect of tamoxifen, but there are few related studies considering the prevalence rate. The purpose of this study was to determine the effect of tamoxifen on the development or aggravation of fatty liver and to identify risk factors in large patient populations.

Methods: This was a single-center, retrospective study performed from January 2007 to July 2017. Consecutive 911 patients were classified into three groups according to the treatment method; tamoxifen group, aromatase inhibitor (AI) group, and control group. Propensity score matching method was used between the groups. The incidence or severity of fatty liver was judged by non-contrast computed tomography or abdominal ultrasound.

Results: Median treatment duration was 49 months and the median observational period was 85 months. Tamoxifen significantly increased fatty liver development or aggravation compared to AI or control groups [hazard ratio (HR) 1.598, 95% confidence interval (CI) 1.173-2.177, *P*=0.003] after adjusting other factors. When subgroup analysis was performed depending on basal fatty liver status, tamoxifen had more effect on fatty liver aggravation (HR 2.103, 95% CI 1.156-3.826, *P*=0.015). However, the development or aggravation of fatty liver did not significantly increase the mortality of breast cancer patients.

Conclusions: Tamoxifen significantly increases the development or aggravation of fatty liver compared to other treatments in breast cancer patients. Therefore, when tamoxifen is used for a long-term period, close monitoring for fatty liver is necessary, especially in high-risk patients, *e.g.* basal fatty liver or high body mass index.

Keywords: Nonalcoholic fatty liver disease, Tamoxifen, Aromatase inhibitor

O-059

Combined Use of Rosuvastatin and Ezetimibe Improves Hepatic Steatosis in Patients with Dyslipidemia

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[1]Department of Internal Medicine, Yonsei University College of Med-

icine, Seoul, Republic of Korea, [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: Rosuvastatin and ezetimibe are beneficial for dyslipidemia control. We investigated whether the combined use of rosuvastatin and ezetimibe improves hepatic steatosis (HS) in patients with dyslipidemia.

Methods: Between January and August 2018, 114 patients with dyslipidemia treated with 6-month combined use of rosuvastatin and ezetimibe were considered eligible for this retrospective cohort study. The degree of HS was assessed using the hepatic steatosis index (HSI). The HS improvement was defined as ≥ 5% reduction in the HSI score from the baseline. The presence of fatty liver was defined as HSI ≥36.

Results: The mean age of the study population (50 men and 64 women; 49 non-diabetic and 65 diabetic) was 57.4 years. The mean body mass index, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and HSI was 25.1 kg/m^2, 207.4 mg/dL, 126.1 mg/dL, 52.9 mg/dL, 146.4 mg/dL, and 36.1, respectively. During 6-month treatment, HS burden was similarly maintained (mean HSI=36.3 at 3 months and 36.4 at 6 months; all *P*>0.05 vs. baseline). On multivariate analyses, ultrasonographic fatty liver (hazard ratio [HR]=3.212, 95% confidence interval [CI] 1.041-9.913) and HSI ≥ 36 (HR=3.501, 95% CI 1.226-10.001) were selected as independent predictors of HS improvement (all *P*<0.05). However, when 53 (46.5%) patients with fatty liver (HSI>36) were selected, HS burden was significantly improved (mean HSI=40.8 at baseline → 39.3 at 3 months → 39.7 at 6 months; all *P*<0.05 vs. baseline).

Conclusions: The combined use of rosuvastatin and ezetimibe for dyslipidemia control did not improve HS burden in all patients with dyslipidemia, but improved HS burden in the subgroup with fatty liver.

Keywords: Rosuvastatin, Ezetimibe, Dyslipidemia, Diabetes mellitus

O-060

Weight Change and Resolution of Fatty Liver in Normal Weight Individuals with Non-Alcoholic Fatty Liver Disease

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Aims: Obesity is a well-known risk factor for non-alcoholic fatty liver disease (NAFLD), and weight reduction is primarily recommended for managing the disease. However, some NAFLD patients show normal weight (lean NAFLD), and whether weight reduction can be recommended for lean NAFLD individuals remains unclear. We investigated the association between weight changes and resolution of fatty liver in patients with NAFLD.

Methods: We conducted a retrospective cohort study of 16,738 adult men and women (average age, 50.5 y; lean NAFLD, 2,383 participants) with NAFLD at baseline who underwent repeated health check-up examinations including body weight measurements and abdominal ultrasonography from January 2003 through December 2013. NAFLD was defined by ultrasonography and exclusion of secondary causes.

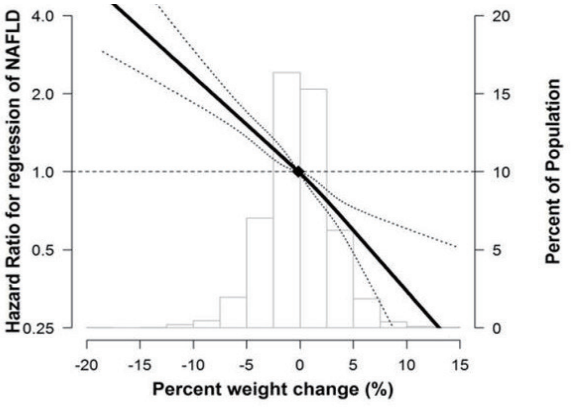

Figure 1. Multivariable-adjusted hazard ratios (95% CI) for fatty liver resolution by percent weight change between visits (%) among lean NAFLD patients

The curves represent adjusted hazard ratios (solid line) and their 95% confidence intervals (dashed lines) for fatty liver resolution based on restricted cubic splines for percent weight change with knots at the 5th, 35th, 65th and 95th percentiles of their sample distributions. The reference value (diamond dot) was set at the 50th percentile. The model was adjusted for age, sex, year of visit, smoking (never, former, current, and missing), alcohol (none, moderate, and missing), body mass index, systolic blood pressure, fasting glucose, total and HDL cholesterol, triglycerides, use of antidiabetic medications, use of antihypertensive medications, and use of lipid lowering medications.

Table 1. Fatty liver resolution rates according to weight changes between visits in NAFLD patients by baseline body mass index (N = 16,738)

Weight change between visits	Normal weight HR (95% CI)	Overweight/obese HR (95% CI)	P for interaction
No reduction or increased	*Reference*	*Reference*	<0.001
>0 ~ 4.9 % reduction	1.40 (1.23, 1.60)	1.75 (1.63, 1.87)	
5 ~ 9.9 % reduction	2.09 (1.68, 2.61)	3.68 (3.37, 4.03)	
10 % or more reduction	2.70 (1.72, 4.24)	6.12 (5.33, 7.02)	
P-value	<0.001	<0.001	

Adjusted for age, sex, year of visit, smoking (never, former, current, and missing), alcohol (none, moderate, and missing), body mass index, systolic blood pressure, fasting glucose, total and HDL cholesterol, triglycerides, use of antidiabetic medications, use of antihypertensive medications, and use of lipid lowering medications

Results: During 68,389 person-years of follow-up (median follow-up of 3.00 years), 5,819 patients had fatty liver resolution. Compared with participants who had no weight reduction or

increased weight, the fully adjusted hazard ratios for fatty liver resolution in participants with 0–4.9%, 5–9.9%, and 10% or more weight reduction were 1.67 (95% confidence interval [CI] = 1.57, 1.77), 3.36 (95% CI= 3.09, 3.65), and 5.50 (95% CI= 4.83, 6.27), respectively. The association between weight reduction and fatty liver resolution was stronger in overweight/obese NAFLD participants but was also evident in lean NAFLD participants in a dose-dependent manner. In spline regression models, the association between weight change and the fatty liver resolution was linear among participants with normal weight.

Conclusions: In a large cohort of NAFLD participants, weight reduction showed a dose-dependent effect on fatty liver resolution in lean NAFLD participants. Lean NAFLD might be considered for metabolically obese individuals who may benefit from weight reduction.

Keywords: Lean, Weight change, Non-alcoholic fatty liver disease

10. Liver Transplantation

June 22, 2019

O-061

Risk Factors for Long-Term Mortality in Live Liver Donors

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Aims: Long-term outcome in live liver donors remains in question. The aim of this study was to evaluate the long-term survival outcome and related factors of live liver donors in Korea.

Methods: Liver donors who were registered in the Korean Network Organ Sharing (KONOS) between February 2000 and December 2015 were included in this study.

Results: During the observation period, there were 52 deaths among 10,116 live liver donors. Median (interquartile range) follow-up was 5.71 (2.88-9.35) years. Univariate analyses showed that factors significantly associated with mortality after donation were individuals aged 50 to 59 years (HR 6.19, 95% CI 2.78–13.79, *P*<0.001), aged 60 years or older (HR 16.49, 95% CI 3.82–71.17, *P*<0.001), and divorced people (HR 7.13, 95% CI 2.81–18.10, *P*<0.001). Unemployed people (HR 9.39, 95% CI 2.51–35.09, *P*=0.001) and office workers (HR 3.82, 95% CI 1.27–11.52, *P*=0.017) were also associated with higher rates of long-term death compared with students. Donor sex, blood type, BMI, smoking or alcoholic habit, level of education, center volume, graft type, donor operation time, year of operation, recipient age, and recipient death were not significantly associated with mortality after donation (*P*>0.05). Multivariate analyses showed divorce (HR 7.075, 95% CI 2.57– 19.51, *P*<0.001) and unemployment (HR 6.969, 95% CI 1.73– 28.1, *P*=0.006) were significant factors of mortality after donation.

Conclusions: Careful health checkup should be continued and long-term risk information and informed consent should be given especially in live liver donors with risk factors.

O-062

Gene Expression of STAT3 and IL-17/Th-17 Pathway Decrease in Tolerance Patients Compared to Non-Tolerance after Tapering Immunosuppressants in Liver Transplantation

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Aims: Finding monitoring markers for immune tolerance during tapering immunosuppressive (IS) drugs is crucial for patients with liver transplantation (LT). In our previous study, we demonstrated that the ratio of regulatory T (Treg) and helper T (Th)17 cells was increased in tolerant patients. In this study, we aimed to find the correlation of the change of Treg/Th17 ratio and gene expression in tolerant and non-tolerant patients.

Methods: We performed a prospective pilot study including 70 LT recipients without rejection and more than 3 years after LT. Among 70 clinically stable patients, 14 most immunologically stable patients were chosen by checking 30 immune markers. The doses of IS drugs given to these 14 LT recipients were tapered over time. After finishing tapering IS, we compared the change of the Treg/Th17 ratio with the change of gene expression using gene-microarray analysis in tolerant and non-tolerant patients.

Results: Of the 14 tapering group patients, seven (50%) had been stable during minimization and/or stopping immunosuppression in the study. After tapering IS drugs, tolerant group maintained increased level of Treg/Th17, Th1/Th17 and CD8/

Th17 ratio than nontolerant group. The levels of gene expression related to the signal transducer and activator of transcription 3 (STAT3) pathway including hypoxia-inducible factor 1α (HIF-1 α), CCL2, Pim1, Fos-related antigen 1 (FRA1) were more decreased in tolerant patients compared to non-tolerant patients. Moreover, Retinoic-acid-orphan-receptor-C (RORc) which is the regulator of IL-17/Th17 were more decreased in tolerant patients than non-tolerant patients.

Conclusions: This gene analysis in IS drug withdrawal study suggest that increase pattern of Treg/Th17 ratio as tolerance signature is appropriate to the decrease of gene expression associated with STAT3 pathway and IL-17/Th-17 pathway.

Keywords: Liver transplantation, Tolerance, Stat3, Il-17, Regulatory T cell, Helper T 17 cell

O-063

Silent Allograft Fibrosis in 10-Year Post-Transplantation Histology of Pediatric Liver Transplantation: Is It Really Silent?

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Aims: This study sought to analyze factors related to long-term allograft fibrosis in clinically stable pediatric liver transplantation patients.

Methods: Pediatric patients who underwent liver transplantation at Samsung Medical Center from January 1997 to January 2008 were reviewed. Ten-year protocol biopsies were examined by an expert pathologist specializing in liver transplantation. The degrees of inflammation and fibrosis were classified based on Banff criteria and the METAVIR system, respectively. Analysis of risk factors for allograft fibrosis was performed using logistic regression.

Results: Sixty-six clinically silent pediatric patients who underwent 10-year post-transplantation biopsy were included. Protocol biopsy revealed nine cases (13.6%) with a rejection activity index ≥3 based on Banff classification and 31 cases (47.0%) with METAVIR fibrosis stage ≥F1. All the characteristics among the patients were similar except for experience of rejection when classified by Banff criteria (29.4% in normal, 60.9% in indeterminant, and 55.6% in mild rejection, *P*=0.039) and METAVIR staging (34.3% in F0, 36.8% in F1, and 83.3% in F2, *P*=0.009). More than three events with aminotransferase level elevated above 50U/L was the only significant factor for METAVIR ≥F1 (OR=3.351, CI 1.160–9.643, *P*=0.026) However, mean total bilirubin ≥1.0mg/dL during the entire period (OR=10.388, CI 1.414–76.322, *P*=0.021) and experience of rejection (OR=10.403, CI 1.788–60.531, *P*=0.009) were significant risk factors for METAVIR stage F2.

Conclusions: Even in clinically silent pediatric liver transplantation patients, long-term fibrosis occurs frequently, and repeated elevation of aminotransferases was related to METAVIR stages ≥F1, while experience of rejection and elevated mean total bilirubin ≥1.0mg/dL were related to METAVIR stage F2.

O-064

Clinical Features and Prognosis of DIHBS (Diffuse Intrahepatic Biliary Stricture) after Adult ABO-Incompatible Living Donor Liver Transplantation

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Aims: Despite the advancement in desensitization protocol, diffuse intrahepatic biliary stricture (DIHBS), an attenuated form of antibody mediated rejection (AMR), remains an unresolved problem. As a high-volume LT center, we retrospectively review clinical outcome and prognosis of recipients who developed DIHBS after ABOi LDLT.

Methods: From November 2008 to December 2017, total of 497 cases of ABO incompatible LDLT were performed at Asan Medical Center. Among them, twenty-four patients (4.83%) developed DIHBS. Retrospective review of medical records of these patients was carried out.

Results: Median time of diagnosis for DIHBS after ABOi LDLT was 2.8 months. In patients with DIHBS, the 3-year patient survival rate was 69.9%. Causes of patient death in nine patients were recurrent HCC in four patients, biliary sepsis in two patients, graft failure (not associated with AMR) in one patient, post-operative bleeding after re-LT in one patient, and pneumonia in one patient. Nine patients (37.5%) received re-transplantation. Graft survival rates at 3-year was 40.6%. Both patient survival and graft survival rates were significantly lower than ABOi LDLT recipients without DIHBS (both *P*<0.001). Between ABOi LDLT patients with or without DIHBS, there were no significant differences in pre-operative isoagglutinin (IA) titer, post-operative peak bilirubin, AST, ALT, IA titer, and pre- and post-operative frequency of total plasma exchange (TPE).

Conclusions: In this study, DIHBS developed usually before 3 months after ABOi LDLT. DIHBS significantly affects short and long-term outcome in ABOi LDLT. In patients who demonstrated DIHBS, over half of the patient progress to graft failure and need re-LT.

O-065

Impact of the Baseline Anti-A/B IgG Titer on the Clinical Outcome in ABO-Incompatible Liver Transplantation

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Aims: The use of ABO incompatible (ABOi) living donors is an attractive solution for expanding the liver donor pool. We investigated the impact of the baseline anti-A/B IgG titer on the transplant outcomes in ABOi liver transplantation (LT).

Methods: We analyzed 394 adult patients who underwent living donor LT (303 ABO compatible LT and 91 ABOi LT) between 2012 and 2018. ABOi LT patients were categorized by baseline IgG titer: low IgG titer (≤ 1:64, n=51) versus high IgG titer (≥ 1:128, n=40). All ABOi LT patients received desensitization therapy including rituximab and plasmapheresis.

Results: Patients with high IgG titer experienced antibody rebound (≥ 1:64) more frequently than those with low IgG titer during the first month after LT (35.0% vs. 15.7%, *P*=0.033). Patient survival rates for ABO compatible, low IgG titer, and high IgG titer were 85.0%, 91.5%, and 74.4%, respectively, at 3 years post-transplantation (*P*=0.006). High IgG titer (HR, 2.76; 95% CI, 1.39-5.48; *P*=0.004) and MELD score of >20 (HR, 2.32; 95% CI, 1.22-4.41; *P*=0.010) were independent risk factors for mortality. Infection was the leading causes of death in all groups, but the proportion was significantly higher in high IgG titer group than in other groups (81.8% vs. 30.8% vs. 33.3%).

Conclusions: Patients with high IgG titer (≥1:128) are associated with a higher risk of death after ABOi LT than those with low IgG titer (≤1:64). Thus, ABOi LT patients with high IgG titer should be managed with great care.

Keywords: Liver transplantation, ABO incompatibility, Desensitization

O-066

Comparative Analysis of Bile Microbiology and Antibiotic Susceptibilities between Liver Transplant Recipients and Normal Population: Multicenter Cohort Study

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Aims: Biliary complications are still unresolved problems after liver transplantation (LT), up to 28%-32%, especially in living donor LT. Effective antibiotics should be administered to control the cholangitis, however immunosuppression after LT may have changed the microbiology of infected bile. The aim of this study was to compare bile microbiology and antibiotic susceptibilities between liver transplant recipients and normal population.

Methods: Between 2008 and 2017, the microbiologic culture and antibiotics sensitivity tests were compared on the patients who underwent percutaneous trans-hepatic biliary drainage because of biliary complications after LT (n=59) and cholecystectomy under the diagnosis of gallbladder disease (n=271) at multiple centers.

Results: The most frequently isolated microorganisms were similar between two groups; Enterococcus (42.4% vs. 29.4%) followed by Escherichia (22.0% vs. 19.0%), Pseudomonas (16.9% vs. 8.8%), and Klebsiella (10.2% vs. 10.1%). For Enterococcus and Escherichia, two most frequently isolated organisms, gentamycin and imipenem showed similar high sensitivity for both organisms in two groups. According to the period, within or after 6 month of LT, Enterococcus (23.7% vs. 18.6%) was consistently frequently isolated, but others were different; Klebsiella (8.5% vs. 1.7%), Escherichia (3.4% vs. 18.6%) and Pseudomonas (3.4% vs. 13.6%).

Conclusions: Microbiologic culture and antibiotics sensitivity tests were similar between liver transplant recipients and normal population, however there was some difference of frequent isolated microorganisms by the period after LT.

Keywords: Bile microbiology, Antibiotic susceptibilities, Liver transplant

11. HBV

O-067

Dynamics of Transient Elastography-Based Risk Prediction Model for Hepatocellular Carcinoma during Antiviral Therapy in Patients with Chronic Hepatitis B: A Nation-Wide Multi-Center Retrospective Cohort Study

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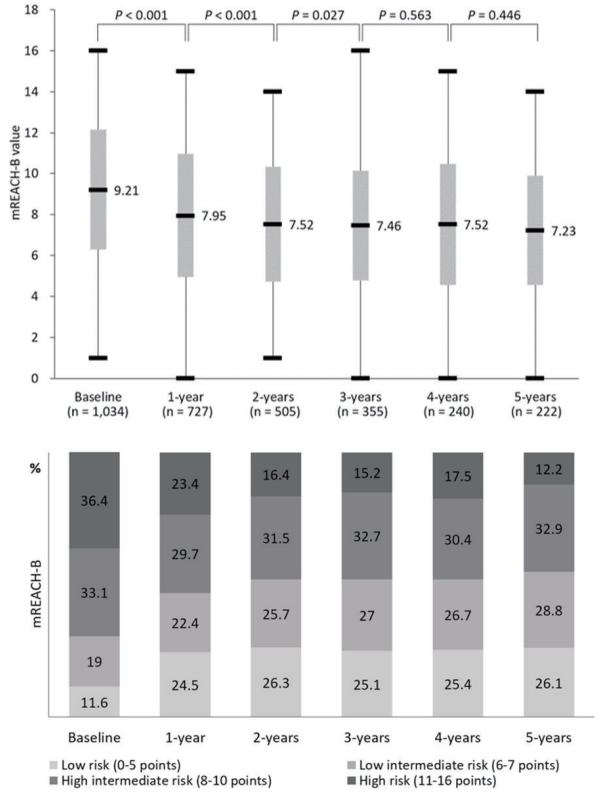
Aims: The transient elastography (TE)-based risk prediction models predict hepatocellular carcinoma (HCC) development. We investigated the influence of antiviral therapy (AVT) on TE-based risk prediction model in patients with chronic hepatitis B (CHB).
Methods: Patients with CHB who initiated AVT were retrospectively recruited from 13 referral Korean institutes. The mREACH-B model was selected for the analysis.



Results: Between 2007 and 2015, 1,034 patients with CHB (729 with entecavir; 305 with tenofovir) were recruited. The mean age of the study population (639 men and 395 women) was 46.8 years. During AVT, the mREACH-B score significantly decreased from the baseline to 3 years of AVT (mean 9.21 → 7.46, *P*<0.05) and was maintained until 5 years of AVT (mean 7.23, *P*>0.05). The proportion of high-risk patients (mREACH-B score ≥11) was significantly reduced from the baseline to 2 years of AVT (36.4% → 16.4%, *P*<0.001) and was maintained until 5 years of AVT (12.2%, *P*>0.05). The mREACH-B scores at baseline, 1 year, and 2 years of AVT independently predicted HCC development (hazard ratio=1.199-1.262) (all *P*<0.05). The cumulative incidence rate of HCC was significantly different at 5 years of AVT among risk groups (high *vs*. high-intermediate *vs*. low-intermediate *vs*. low) from baseline (4.5% *vs*. 3.2% *vs*. 1.5% *vs*. 0.8%) and 1 year (11.8% *vs*. 4.6% *vs*. 1.8% *vs*. 0.6%) (all *P*<0.05, log-rank tests).
Conclusions: The mREACH-B score was dynamically changed during AVT. Thus, repeated assessment of the mREACH-B score is required to predict the changing risk of HCC development in patients with CHB undergoing AVT.

Keywords: Transient elastography, Risk prediction, Hepatocellular carcinoma, Chronic hepatitis B

O-068

Increased Clinical and Economic Burden of Chronic Hepatitis B (CHB) Patients Compared to Non-CHB from 2007 to 2016 in Korea

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Aims: CHB prevalence in Korea ranges from 2-7% and is attributable for ~64-70% of hepatocellular carcinoma (HCC) cases. This study aims to characterize the distribution and trend in demographics and comorbidity among CHB patients in Korea between 2007 and 2016.
Methods: We used the Health Insurance Review & Assessment Service (HIRA) Database to identify patients ≥18 years with CHB as identified by ICD-10 codes (B18.1). Demographic and comorbidity data was reported cross-sectionally for 2007, 2011, and 2016. Cases and non-CHB controls were matched in a 1:4 ratio using propensity score matching method.
Results: A total of 253,002 patients met inclusion and exclusion criteria in 2007, with 320,245 in 2011 and 418,099 patients in 2016. The mean age of patients was 47 years (SD 13.3) in 2007 and increased to 52 years (SD 12.5) in 2016 (*P*<0.0001). As shown in Table 1, by 2016, CHB patients in Korea had significantly (*P*<0.001) higher comorbidity burden compared to matched non-CHB with (37% with hyperlipidemia, 29% with hypertension, 20% with diabetes, 4% with osteoporosis/bone fracture, and 3% with chronic kidney disease ; all of which have increased significantly from 2007 (all *P*<0.001). The average Devo-Carlson comorbidity index (DCCI) was also calculated and the score was higher in CHB group compare to matched control group (2.22 vs 1.15, *P*<0.0001). In addition, CHB patients showed a higher prevalence of concomitant medication and had significantly higher rates of health care resource utilization (HCRU), such as hospitalization and outpatient visits, compared to non-CHB patients, which significantly increased

over time from 2007 to 2016 (*P*<0.001).

Table 1 Comorbid conditions and concomitant medication of CHB and matched controls

Variables	CHB			*P* for trend*	Matched controls			*P* for trend*	*P* value**		
	2007 n (%)	2011 n (%)	2016 n (%)		2007 n (%)	2011 n (%)	2016 n (%)		2007	2011	2016
Total N	253,002	320,245)	418,099		1,012,008	1,280,980	1,672,396				
Comorbidity											
CVD	10,378(4.10)	13,419(4.19)	20,143(4.82)	<0.001	32,862(3.25)	49,553(3.87)	77,366(4.63)	<0.001	<0.001	<0.001	<0.001
CKD	5,119(2.02)	7,706(2.41)	12,623(3.02)	<0.001	6,312(0.62)	9,965(0.78)	19,040(1.14)	<0.001	<0.001	<0.001	<0.001
Cirrhosis	47,316(18.7)	56,993(17.8)	72,216(17.27)	<0.001	4,298(0.42)	4,580(0.36)	5,858(0.35)	<0.001	<0.001	<0.001	<0.001
DCC	16,367(6.47)	16,843(5.29)	16,073(3.84)	<0.001	1,911(0.19)	2,216(0.17)	2,713(0.16)	<0.001	<0.001	<0.001	<0.001
Diabetes	45,487(17.98)	57,149(17.85)	82,290(19.68)	<0.001	84,922(8.39)	129,605(10.12)	217,000(12.98)	<0.001	<0.001	<0.001	<0.001
HCC	18,067(7.14)	25,286(7.90)	34,408(8.23)	<0.001	1,044(0.10)	1,246(0.10)	1,672(0.10)	0.5841	<0.001	<0.001	<0.001
Hypertension	60,243(23.81)	81,339(25.4)	122,868(29.39)	<0.001	175,840(17.38)	269,921(21.07)	422,657(25.27)	<0.001	<0.001	<0.001	<0.001
DLP	48,683(19.24)	77,846(24.31)	155,670(37.23)	<0.001	90,537(8.95)	186,039(14.52)	397,573(23.77)		<0.001		
Osteoarthritis	34,892(13.79)	49,005(15.30)	85,644(20.48)	<0.001	125,934(12.44)	185,394(14.47)	325,790(19.48)	<0.001	<0.001	<0.001	<0.001
OP Fracture†	6,875(2.72)	11,222(3.50)	17,097(4.09)	<0.001	21,521(2.13)	37,637(2.94)	53,971(3.23)	<0.001	<0.001	<0.001	<0.001
Deyo-Charlson Comorbidity Index††	2.30±2.60	2.12±2.38	2.22±2.33	<0.001	0.85±1.42	0.96±1.47	1.15±1.61	<0.001	<0.001	<0.001	<0.001
Concomitant medication											
Antidiabetic medication	30,751(12.15)	42,577(13.3)	60,004(14.35)	<0.001	69,708(6.89)	110,343(8.61)	178,560(10.68)	<0.001	<0.001	<0.001	<0.001
Lipid lowering agent	23,258(9.19)	38,947(12.16)	78,307(18.73)	<0.001	78,261(7.73)	168,387(13.15)	357,425(21.37)	<0.001	<0.001	<0.001	<0.001
Hypertension mediation	67,622(26.73)	93,405(29.17)	131,362(31.42)	<0.001	198,652(19.63)	304,465(23.77)	457,245(27.34)	<0.001	<0.001	<0.001	<0.001
Diuretic											<0.001
OP medication	22,924(9.06)	24,443(7.63)	23,011(5.50)	<0.001	17,982(1.78)	21,204(1.66)	28,355(1.70)	<0.001	<0.001	<0.001	<0.001
NSAIDs	190,116(75.14)	242,282(75.66)	324,451(77.60)	<0.001	790,850(78.15)	1,011,111(78.93)	1,348,458(80.63)	<0.001	<0.001	<0.001	<0.001
Corticosteroid	118,553(46.86)	167,667(52.36)	238,224(56.98)	<0.001	457,191(45.18)	649,332(50.69)	927,628(55.47)	<0.001	<0.001	<0.001	<0.001

CVD: Cerebrovascular disease; CKD: Chronic kidney disease; DCC: Decompensated cirrhosis; HCC: Hepatocellular carcinoma; DLP: Dyslipidemia; OP Fracture: Osteoporosis Fracture; NSAIDs: Nonsteroidal anti-inflammatory drug

† Patients who had 1 or more hospitalizations, or 2 or more outpatients for OP Fracture and who had OP medications

†† Deyo-Charlson Comorbidity Index was calculated excluding CHB disease score, and expressed as mean ± SD.

*P-values for time trend within the group were calculated from simple linear regression for continuous variables and Cochran-Armitage trend test for categorical variables

**P-values were calculated from one-way ANOVA with repeated measures for continuous variables and generalized estimating equations for categorical variables between CHB and matched controls

Conclusions: Between 2007-2016, the Korean CHB population has significantly aged with more comorbidities, and HCRU including renal and metabolic bone disease that may affect CHB management. As CHB treatment is lifelong, careful selection of NUCs treatment and monitoring should be considered in aging Korean CHB populations.

Keywords: Comorbidity, HBV, Burden of HBV, Increased clinical and economic burden

O-069

Comparison of Tenofovir and Entecavir on the Risk of Hepatocellular Carcinoma and Liver-Related Events in Patients with Chronic Hepatitis B: A Propensity Score Analysis

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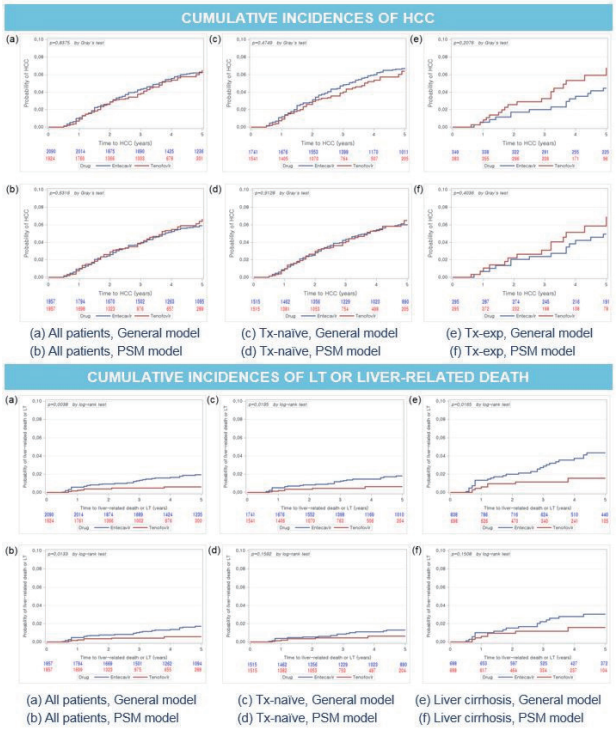
Aims: The use of tenofovir (TDF) and entecavir (ETV) in chronic hepatitis B (CHB) patients has led to a decrease in the incidence of hepatocellular carcinoma (HCC) and liver-related events. However, whether there is a difference between the two highly-potent agents in the extent of improving such clinical outcomes has not been clarified thus far. Therefore, we aimed to compare the effects of TDF and ETV on the risk of HCC and liver-related events.

Methods: A total of 7,015 consecutive CHB patients who were treated with TDF or ETV between February 2007 and January 2018 at the liver units of the Catholic University of Korea were screened for study eligibility and 4,014 patients were finally analyzed. Primary endpoints were HCC and occurrence of liver-related events within 5 years after the initiation of antiviral therapy. Liver-related event was defined as either liver transplantation (LT) or liver-related death.

Results: No difference was observed between TDF and ETV in the incidence rates of HCC in the entire cohort (HR, 1.047; 95% CI, 0.780-1.406, PSM model, *P*=0.757) and subgroups of treatment-naïve, treatment-experienced, chronic hepatitis and cirrhotic patients. However, TDF significantly lowered the risk of liver-related events compared to ETV in the entire cohort (HR, 0.380; 95% CI, 0.173-0.834, PSM model, *P*=0.015).



Conclusions: This study has demonstrated the intermediate-term clinical outcomes in CHB patients who received TDF or ETV treatment. There was no difference in the risk of HCC between the two drugs but TDF significantly lowered the risk of liver-related events compared to ETV.

Keywords: Tenofovir, Entecavir, Hepatocellular carcinoma, Chronic hepatitis B

O-070

The Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Who Received Tenofovir vs. Entecavir Treatment

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Aims: A recent study suggested patients received tenofovir disoproxil fumarate (TDF) treatment have a lower risk of hepatocellular carcinoma (HCC) than those received entecavir (ETV).

We aimed to compare TDF and ETV on the risk of HCC in a territory-wide cohort of patients with chronic hepatitis B (CHB).

Methods: Consecutive adult CHB patients who were initially treated with ETV or TDF for at least 6 months between January 2008 and June 2018 were identified using Clinical Data Analysis and Reporting System in Hong Kong. Patients who had cancers or liver transplantation before or within the first 6 months of treatment were excluded. Missing data were replaced by multiple imputation. Propensity score (PS) weighting was used after multiple imputation to balance the clinical characteristics between two treatment groups; PS included all covariates in the multivariable analysis, serum creatinine, and renal replacement therapy. Fine-Gray model was used to adjust for competing risk of death.

Results: 29,350 CHB patients were identified. Their mean age was 52.9±13.2 years, 18,685 (63.7%) were male; 1,309 (4.5%) and 28,041 (95.5%) first received TDF and ETV, respectively. TDF-treated patients were younger (43.2 *vs.* 53.4 years) and less likely to be cirrhotic (35 [2.7%] *vs.* 3,650 [13.0%]). At a median (interquartile range) follow-up of 3.6 (1.7–5.0) years, 8 (0.6%) TDF-treated and 1,386 (4.9%) ETV-treated patients developed HCC. The 5-year cumulative incidence (95% confidence interval [CI]) of HCC in TDF-treated and ETV-treated patients was 1.1% (0.5%-2.3%) and 7.0% (6.6%-7.3%), respectively (Figure). TDF use was associated with a lower risk of HCC than ETV use with (weighted subdistribution hazard ratio [SHR] 0.36, 95% CI 0.16-0.80, *P*=0.013) and without (adjusted SHR 0.32, 95% CI 0.16-0.65, *P*=0.002) PS weighting.

Conclusions: TDF treatment is associated with a lower risk of HCC than ETV treatment in a territory-wide cohort of CHB patients.

Keywords: Nucleos(t)ide analogues, Hepatocellular carcinoma, Chronic hepatitis B

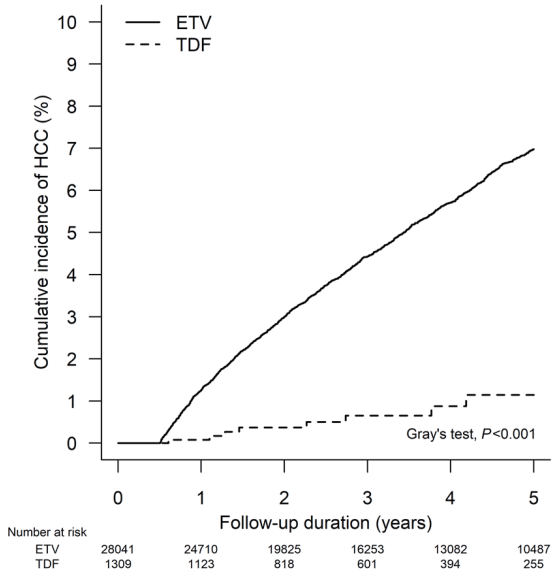

Figure 1.

O-071

Hepatitis B Immunology

Ashish Kumar Vyas[1,4], Pooja Negi[1], Sharda Patra[2], Jaswinder Singh Maras, Shiv Kumar Sarin[3], Nirupma Trehanpati[1*]

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Aims: Vertical transmission of Hepatitis B virus (HBV) from infected mother to the newborn is the main cause of chronicity of HBV infection. However, there is rather scanty information on the role of maternal immunity in maternofetal transmission. Our aim is to understand the role of immunity of HBV infected mother in vertical transmission.

Methods: A total of 18461 pregnant females were screened for HBsAg. Fifty HBsAg+ve pregnant mothers and their newborns were recruited in this study and tested for transmission of HBV (HBsAg, HBV DNA); 22 were positive and rest were negative. PBMCs from the transmitting (Gr. A, n=22) and non-transmitting (Gr. B, n=28) mothers were analyzed for different immune cell subsets by flow cytometry including dendritic cells (DCs), CD4, CD8, TFh and B cells. The HBV-specific responses of different cells were assessed using pooled surface and core overlapping HBV peptides. Next-generation sequencing (NGS) was performed in PBMCs; qRT-PCR and ELISA was performed to validate the flow data.

Results: Mothers in Gr. B then A had higher frequencies and greater HBV specific DC, CD4, CD8, TFh and B cell-mediated protective responses. RNAseq showed increased expression of CD4, CD8, B, TFH, and Immune-related genes in Gr. B compared to Gr. A. Frequency of TFh cells inversely correlated with HBV DNA and IL-21. ROC analysis gave the cut-off values with the highest specificity and sensitivity to predict the involvement of TFh and B cells in HBV vertical transmission.

Conclusions: Serum IL-21 levels, TFh, and plasma B cells are useful predictors of vertical transmission of HBV from infected mothers to the newborns. Our study first time showed defective maternal immunity influences the chances of HBV transmission into their newborns. These cells can be used as a therapeutic target for protection of vertical transmission.

Keywords: Hepatitis B, Vertical transmission, Immune responses, T follicular helper cells

O-072

Sustained Response without Nucleos(t)Ides after Pegylated Interferon Represent Favorable Outcome: Up to 13 Years Follow-Up

Soon Kyu Lee[1], Jung Hyun Kwon[*2], Jeong Won Jang[1], Hee Chul Nam[1], Yoon-Jung Kim[2], Sun Hong Yoo[2], Soon Woo Nam[2], Si Hyun Bae[3], Jong Young Choi[1], Seung Kew Yoon[1]

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Aims: Pegylated interferon (PEG-IFN) treatment with a high rate of off-therapy host immune control is still an attractive treatment for chronic HBV infection. There remains uncertain about the prognosis of sustained responder after PEG-IFN treatment who don't need nuecleos(t)ides (NAs). We investigated the long-term outcomes of PEG-IFN treatment focused on tolerant patients without NAs up to 13 years.

Methods: A consecutive 172 patients treated with PEG-IFN for chronic hepatitis B or compensated liver cirrhosis between 2005 and 2014 were enrolled and finally 122 patients who fully completed PEG-IFN treatment were analyzed. The definition of response for PEG-IFN treatment at 6months post-treatment were as follows: HBeAg positive patients, achieve both virologic response (VR, <2,000 IU/ml of HBV DNA) and serologic response (HBeAg loss or seroconversion); HBeAg negative patients, reach VR. During follow-up period, we analyzed the number of patients with HBsAg loss, starting NAs due to viral activation and disease progression including liver cirrhosis and hepatocellular carcinoma (HCC).

Results: The median follow-up period of 122 patients were 7.2 years (range, 1.1 -13.2 years). Of 122 patients, 43 patients (35.2%) had a response at 6 months post-treatment. During follow-up, 69 patients (56.6%) started NAs and the patients who had a response for PEG-IFN significantly lower rate of starting NAs (14/43 vs 55/79, *P*<0.001). HBsAg loss occurred in 9 patients (7.4%) and sustained responders without further NAs treatment had significantly high rate of HBsAg loss compared to the patients with starting NAs (13.2% vs. 2.9%, *P*=0.01). Eight patients (6.6%) developed disease progression including HCC (n=3). All of them were non-sustained responders who started NAs after PEG-IFN therapy compared to sustained responders (*P*=0.03).

Conclusions: Sustained responders without further NAs treatment after PEG-IFN treatment had a favorable clinical outcome in HBsAg loss and no disease progression up to 13 years.

Keywords: Pegylated interferon, HBV, HCC, Liver cirrhosis, Nucleos(t)ides, HBsAg loss

12. Liver Cancer,Clinical

O-073

Novel Deep Neural Network-Based Liver Transplantation Criteria for Hepatocellular Carcinoma: A Multicenter Study

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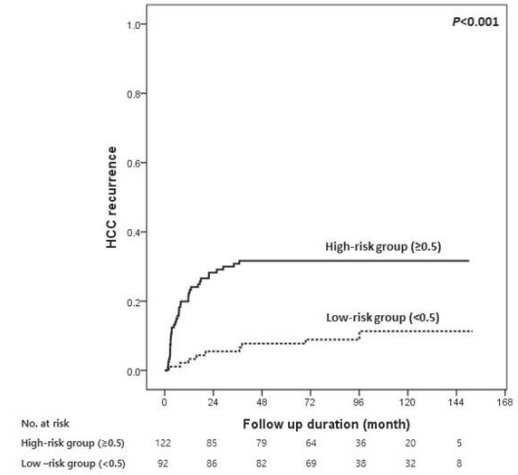
Aims: Because recent data suggest that Milan criteria (MC) may be too conservative, several models have been developed for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). This study aimed to develop new criteria using deep learning for LT in patients with HCC.

Methods: This study included 563 patients who underwent LT for HCC without evidence of extrahepatic metastasis at three referral hospitals in Korea. The derivation cohort consisted of 349 patients (who underwent LT at Samsung Medical Center or National Cancer Center) and the validation cohort included 214 patients (at Seoul National University). The primary outcome was time-to-recurrence after LT. A novel model was developed using the derivation cohort with residual-block-based deep neural network (DNN), and its performance was validated using the validation cohort.



Results: The median follow-up was 78.1 (interquartile range, 39.0–110.5) months. The 203 patients (36.1%) had HCC exceeding MC and portal vein invasion was observed in 83 (14.7%). The optimal model consisted of seven layers including two residual-blocks. Through the performance assessment in validation cohort, DNN model showed better discrimination

function compared to MC (c-index: 0.75 vs. 0.64), and calibration was confirmed by Hosmer-Lemeshow test (P>0.05). The high-risk group (probability cut-off≥0.5) presented significantly higher tumor-recurrence rate than low-risk group (cut-off<0.5) in the validation cohort (hazard ratio, 2.67; 95% confidence interval, 1.36–5.25; P<0.001; see Figure). The expected probabilities of tumor recurrence at years 1, 3, and 5 were 7.0%, 12.0%, and 12.0% in low-risk group; and 27.4%, 29.7%, and 30.9% in high-risk group, respectively. The largest weighted parameter in DNN model was tumor size and followed by alpha-fetoprotein, age, and PIVKA-II.

Conclusions: The DNN model presented better prediction ability of tumor-recurrence after LT than MC. New model is considered as optimal LT criteria in HCC patients, in that it can evolve with further data.

Keywords: Deep learning, Milan criteria, Liver transplantation, Hepatocellular carcinoma

O-074

Bioelectrical Impedance Analysis for Predicting Postoperative Complications and Survival after Liver Resection for Hepatocellular Carcinoma

Gil Ho Lee[1], Hyo Jung Cho[1], Garam Lee[1], Han Gyeol Kim[1], Hee Jung Wang[2], Bong Wan Kim[2], Mi Young Lee[1], Jin Hee Cheong[1], Young Hwan Ahn[1], So Young Yoon[1], Choong Kyun Noh[1], Chul Won Suh[3], Jung Woo Eun[1], Jae Youn Cheong[1], Sung Won Cho[1], and Soon Sun Kim[1]

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Aims: Bioelectrical impedance analysis (BIA) provides information on body composition and nutritional status in patients with cancer. However, it is unclear whether the preoperative edema index or phase angle, obtained from BIA, predicts postoperative complication or mortality in patients with hepatocellular carcinoma (HCC). Thus, we investigated whether preoperative BIA could predict postoperative complications and survival in patients with HCC.

Methods: Seventy-nine patients who underwent liver resection for HCC were prospectively enrolled and BIA was performed before surgery. The development of postoperative ascites or acute kidney injury (AKI) and patients' survival were monitored after surgery.

Results: Among 79 patients, 35 (44.3%) developed ascites or AKI after liver resection. In multivariate analysis, a high preoperative edema index (extracellular water/total body water) (>0.384) (odds ratio 3.96; 95% confidence interval 1.03-15.17; P=0.045) and higher fluid infusion during surgery (odds ratio 1.36; 95% confidence interval 1.04-1.79; P=0.026) were identified as significant risk factors for ascites or AKI after hepatectomy. Subgroup analyses showed that the edema index was a significant predictor of ascites or AKI in patients with cirrhosis but not in those without cirrhosis. Tumor size was the only significant predictive factor for short-term survival after hepatectomy.

Conclusions: The preoperative edema index using BIA can be used as a predictor of post-hepatectomy complication, especially in patients with liver cirrhosis.

Keywords: Electric impedence, Ascites, Acute kidney injury, Carcinoma, Hepatocellular, Hepatectomy

O-075

Laparoscopic Resection vs. Percutaneous Radiofrequency Ablation for Small Single HCC: Comparison of Clinical Outcome

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Aims: To compare laparoscopic liver resection (LLR) and percutaneous radiofrequency ablation (p-RFA) as first-line treatment options in patients with single nodular hepatocellular carcinomas (HCCs) ≤ 3 cm.

Methods: A total of 566 patients treated by either LLR (n=251) or p-RFA (n=315) were included. The recurrence-free survival (RFS) and cumulative incidence of local tumor progression (LTP) were estimated using Kaplan-Meier methods and compared using the log-rank test. Treatment outcome of two treatment modalities was compared in subgroup of patients according to tumor location.

Results: There were no significant differences in overall survival between LLR and p-RFA (P=0.160), however, 3-year RFS was demonstrated to be significantly higher after LLR (74.4%) than after p-RFA (66.0%) (P=0.013), owing to its significantly lower cumulative incidence of LTP (2.1% at 3-years after LLR vs. 10.0% after p-RFA, P<0.001). LLR also provided significantly better local tumor control than p-RFA for subscapular tumors (3-year LTP rates: 1.9% vs. 8.8%, P=0.012), perivascular tumors (3-year LTP rates: 0.0% vs. 17.2%, P=0.007), and tumors located in antero-lateral liver portions (3-year LTP rates: 0.0% vs. 10.7%, P<0.001). However, there were no significant differences in LTP rates between LLR and p-RFA for non-subcapsular and non-perivascular tumors (P=0.482) and for tumors in postero-superior liver portions (P=0.380).

Conclusions: LLR can provide significantly better local tumor control than p-RFA for small single HCCs in subcapsular, perivascular, and anterolateral liver portions, and thus may be thepreferred treatment option for these tumors.

Keywords: Hepatocellular Carcinoma, Radiofrequency ablation, Laparoscopic liver resection, Local tumor progression

O-076

Factors and Models for Predicting Liver-Related Morbidity in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma

Jonggi Choi[1*], So-hyun Kim[2*], Seungbong Han[3], Danbi Lee[1], Ju Hyun Shim[1], Young-Suk Lim[1], Han Chu Lee[1], Young-Hwa Chung[1], Yung-Sang Lee[1], Sung-Gyu Lee[4], Ki-Hun Kim[4], and Kang Mo Kim[1]

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Aims: Hepatic resection has been a main treatment option for patients with hepatocellular carcinoma (HCC). The aim of this study was to seek predictive factors and to build predictive model for liver-related morbidity after liver resection for HCC.

Methods: A total of 1,565 patients who underwent liver resection for HCC at Asan Medical Center, between January 2016 and December 2017 were retrospectively analyzed. Laboratory tests were assessed before, and 1,2,3,5,7, and 10 days after surgery. Post-hepatectomy biochemical dysfunction (PHBF) was defined as increased INR > 1.5 or hyperbilirubinemia > 2.9 mg/dL on or after postoperative day (POD) 5. If INR or bilirubin level had increased preoperatively, PHBF was defined as increasing INR or serum bilirubin on or after POD 5, compared with the values of the previous days. Definition of post-hepatectomy liver-related morbidity included PHBF, ascites requiring diuretics or invasive drainage procedures, hepatic encephalopathy, rescue liver transplantation, and deaths from any causes within 90 days after operation.

Results: The present study analyzed 1,565 patients who underwent liver resection for HCC, including 1,258 men (80.4%) with a mean age of 58.3 years (Table 1). Major etiology of underlying liver disease was chronic hepatitis B virus infection (80.8%). Patients with cirrhosis comprised of 37.9% of patients. Patients who underwent transarterial chemoembolization (TACE) and portal vein embolization (PVE) before liver resection were 258 (16.5%) and 156 (10.0%), respectively. Of 1,565 patients, 790 (50.5%) underwent right hepatectomy and 271 (17.3%) received left hepatectomy. Segmentectomy was performed in 272 (17.4%) patients and 85 (5.4%) received bisegmentectomy. To build and validate the prediction model, study population was divided into train and test set in a 3:1 ratio. Eight-three (5.3%) patients had a bilirubin > 2.9 mg/dL or INR > 1.5 on or after POD 5. Post-operative ascites requiring diuretics or invasive drainage procedure occurred in 51 (3.3%) patients. One patient developed hepatic encephalopathy resulting from deterioration of liver function. Two patients experienced liver failure subsequently underwent rescue liver transplantation. A total of 13 mortality occurred within 90 days after operation, of which 4 patients died within 30 days. Male (Adjusted odds ratio [AOR]: 2.49, 95% confidence interval [CI]: 1.25-4.97), cirrhosis (AOR: 2.00, 95% CI: 1.27-3.15), major resection (AOR: 2.22, 95% CI: 1.42-3.45), platelet ≥150,000 (AOR: 0.96, 95% CI: 0.44-1.09), serum albumin level ≥3.5 g/dL (AOR: 0.52, 95% CI: 0.32-0.82), and INR (1≤INR<1.1: 1.42 [0.49-4.12], 1.1≤INR<1.2: 1.90 [0.65-5.58], and INR≥1.2: 6.32 [1.97-20.29] were selected as factors for predicting post-operative liver-related morbidity in the training cohort with an area under the receiver operating characteristics of 0.737 (95% CI: 0.689-0.784). Test set was validated with an area under the receiver operating characteristic (AUROC) of 0.740 (95% CI: 0.647-0.833).

Conclusions: We proposed point-based prediction model and points were assigned for sex (male: 3 point), cirrhosis (2 point), major resection (2 point), platelet <150,000 (1 point), serum albumin <3.5 g/dL (2 point), and INR (1.0≤INR<1.1: 1 point, 1.1≤INR<1.2: 2 point, and INR≥1.2: 5 point) based on regression coefficients. The sum of these 6 points enables predictive risk for liver-related morbidity after liver resection for HCC.

Keywords: Liver resection, Hepatocellular carcinoma, Post-hepatectomy, Liver-related morbidity

O-077

Regorafenib versus Nivolumab for Hepatocellular Carcinoma Patients Who Experienced Sorafenib Treatment Failure: A Propensity Score Analysis

Cheol-Hyung Lee[1], Yun Bin Lee[1], Minseok Albert Kim[1], Heejoon Jang[1], Sun Woong Kim[1], Eun Ju Cho[1], Kyung-Hun Lee[2,3], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Tae-You Kim[2,3], Yoon Jun Kim[1*]

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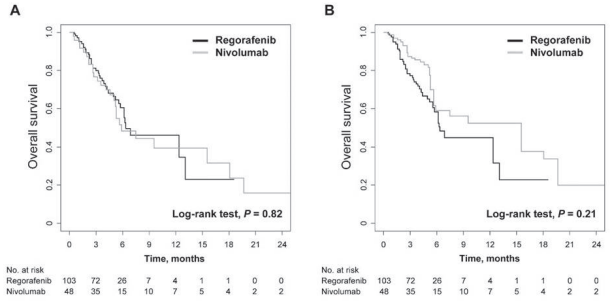
Aims: Several treatment options are now available for patients with hepatocellular carcinoma (HCC) who progress during sorafenib treatment. We aimed to compare the efficacy of regorafenib and nivolumab in HCC patients who have failed sorafenib treatment.

Methods: Consecutive patients who received regorafenib or nivolumab for the treatment of HCC after sorafenib treatment failure between July 2015 and October 2018 at Seoul National University Hospital were included in this retrospective study. Primary endpoint was overall survival. Inverse probability weighting (IPW) using propensity scores was conducted to reduce the treatment selection bias.

Results: Among 151 included HCC patients, 103 patients received regorafenib and 48 patients received nivolumab. During the median (interquartile range) follow-up of 4.1 (2.8–6.2)

months, 66 of 151 patients (43.7%) died: 39 of 103 patients (37.9%) receiving regorafenib and 27 of 48 patients (56.3%) receiving nivolumab. Median survival was 6.4 months (95% confidence interval [CI], 2.4–10.4) for regorafenib and 5.9 months (95% CI, 3.7–8.1) for nivolumab (*P*=0.82 by log-rank test) (Fig. 1A). Overall survival was not significantly different between the groups (nivolumab vs. regorafenib: adjusted hazard ratio [aHR], 0.81; 95% CI, 0.48–1.36; *P*=0.42). Even after balancing baseline characteristics using IPW, overall survival was still similar between the groups (*P*=0.21 by log-rank test) (Fig. 1B). However, patients treated with nivolumab showed significantly prolonged overall survival compared to patients treated with regorafenib (aHR, 0.48; 95% CI, 0.25–0.91; *P*=0.03) after adjusting for baseline characteristics including the levels of alkaline phosphatase, aspartate aminotransferase, and MoRAL score (=11 x sqrt(PIVKA) + 2 x sqrt(AFP)), Child-Pugh class, and the presence of clinically significant portal hypertension.

Figure 1



Conclusions: Improved overall survival was demonstrated in patients who were treated with nivolumab compared to patients who were treated with regorafenib after rigorous adjustment for baseline demographic and clinical characteristics.

Keywords: HCC, Regorafenib, Nivolumab, Survival, Liver cancer

O-078

The Effect of Urea Cream on Sorafenib-Associated Hand-Foot Skin Reaction in Patients with Hepatocellular Carcinoma: Multicenter, Prospective Randomized Double-Blind Controlled Study

Young-Sun Lee[1], Ji Hoon Kim*, Do Young Kim[2], Moon Young Kim[3], Hyung Joon Kim[4], Yeon Seok Seo[1], Ki Tae Yoon[5], Jeong-Hoon Lee[6], Hyun Woong Lee[7], Young Kul Jung[8], Hyung Joon Yim[8], Byoung Kuk Jang[9], Eun Sun Jang[10], Jae Young Jang[11], Sung Bum Cho[12], Sang Youn Hwang[13]

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Aims: Sorafenib has recommended as first line treatment in patients with advanced hepatocellular carcinoma (HCC). Although sorafenib increase overall survival in patients with HCC, it has many side effects such as fatigue, diarrhea, vomitting, nausea, pruritus, depilation,and Hand-Foot Skin Reaction (HFSR). Among them, HFRS is the most common side effect and it is main reason for dose de-escalation or discontinuation of sorafenib in patients with HCC. In this study, we aimed that investigate the role of urea cream in preventing the occurrence of HFSR or ameliorating severity of HFSR.

Methods: Total 288 patients with HCC at 13 hospitals in Korea were randomly assigned from May 2016 to May 2018. Patients were treated with placebo cream and urea cream at the same time as starting the treatment of sorafenib. Patients were followed up for up to 12 weeks. HFSR, score for Hand-Foot Skin Reaction and Quality of Life (HF-QoL) questionnaire, and adverse event were assessed at 2, 4, 8, and 12 weeks.

Results: After exclusion of 41 patients, 247 patients with 117 patients in placebo control group and 130 patients in urea cream group were analyzed. Urea cream group showed lower cumulative incidence of any grade of HFRS (Log-rank, *P*=0.247) and severe HFRS of 2 or more grade Log-rank, *P*=0.394) without statistical significance. In the incidence by time point, development of severe HFRS of 2 or more grade were significant lower in urea cream group compared to placebo control group (13.8% vs. 23.9%, *P*=0.042). Urea cream group showed significant improved score of HF-QoL questionnaire comparing with placebo control group (11.8 vs. 19.7, *P*=0.014) at 12 weeks. There was no significant difference for overall survival (Log-rank, *P*=0.748) between two groups. Tumor response were also not significantly different between two groups, which objective response rate was 6.2% in placebo control group and 6.0% in urea cream group (*P*=0.957), and disease control rate was 44.3% in placebo control group and 42.0% in urea cream group (*P*=0.741).

Conclusions: Treatment of urea cream showed decreased incidence of severe sorafenib-induced HFRS at 2 weeks and decreased tendency of development of HFRS in patients with HCC. Therefore, treatment of urea cream might be considered in patient that treated with sorafenib for HCC.

Keywords: HCC, Sorafenib, Hand-foot skin reaction

13. Cirrhosis & Liver Failure

O-079

Validation of the Updated Version of Korean Stroop Test in the Screening of Minimal Hepatic Encephalopathy

Eileen L. Yoon[1], Dae Won Jun[2], Eun-Chul Jang[3], Jae Yoon Jeong[4], Do Seon Song[5], Sang Bong Ahn[6], Hee Yeon Kim[7], Sung Eun Kim[8], Hyoung Su Kim[9], Soung Won Jeong[10], Sang Gyune Kim[11], Tae Hee Lee[12], Yong Kyun Cho[13]

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Aims: Burden of minimal hepatic encephalopathy (MHE) is significant, but no universal criteria for diagnosis have been established. We aimed to validate the updated version of Korean Stroop Test for MHE screening.

Methods: Liver cirrhosis (LC) patients without history of overt HE were recruited prospectively from 13 centers. All participants completed Korean paper-pencil test (KPPT) and the Korean stroop test. Korean stroop test consisted of two Stroop-off states (color and word) and two Stroop-on states (inhibition and switching). Four types of "On Time + Off Time"s were analyzed (color-plus-inhibition, color-plus-switching, word-plus-inhibition, and word-plus-switching). MHE was diagnosed when KPPT scores ≥ 2.

Results: A total of 119 LC patients and 792 healthy controls were enrolled. The most common etiology of LC was alcohol (62.8%). Mean MELD score of LC patients was 11. Prevalence of MHE was 39.5% by KPPT. Four types of "On Time + Off Time" significantly differed among healthy controls, cirrhosis patients without MHE, and cirrhosis patients with MHE. All types of "On Time + Off Time" showed positive correlation with PHES scores (all P<0.01). The highest area under the curve (AUC) among "On Time + Off Time"s, was for word-plus-inhibition (AUC=0.699, 95% Confidence Interval: 0.603–0.795, P<0.001) in discrimination of MHE. Ln Prothrombin time (INR) (OR 197.33, P=0.008) and word-plus-inhibition (OR 1.012, P=0.011) were significant in multivariate analysis for MHE diagnosis. The cut-off point for the highest Youden's index value was 155 sec for word-plus-inhibition time with 78.8% of sensitivity and 60.6% of specificity. In the subgroup of patients with MELD score less than 11, On Time + Off Time for word-plus-inhibition was the only prognostic factor in the diagnosis of MHE (OR 1.008, P=0.037).

Conclusions: The Korean Stroop Test is simple and valid for screening of MHE.

Keywords: Cirrhosis, Minimal hepatic encephalopathy, Screening, Stroop test

O-080

Validation of Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure (ACLF) Research Consortium (AARC) ACLF Score in Korean ACLF Cohort

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Aims: We aimed to validate the Asian Pacific Association for the Study of the Liver acute-on-chronic liver failure (ACLF) Research Consortium (AARC) ACLF score in Korean ACLF cohort.

Methods: Data from 534 patients who included in the prospective Korean ACLF study and with AARC ACLF score. The diagnostic performances for short-term mortality were compared by the area under the receiver operating characteristic curve (AUROC).

Results: The mean age was 55 years, and 76.4% were male patients. Most patients (91.8%) had cirrhosis, and 29.4% were ACLF patients based on either AARC or European Association for the Study of the Liver (EASL) - chronic liver failure (CLIF) ACLF definition. There were no significant differences between AUROC value of AARC ACLF score (AARC ACLFs) and the AUROC values of other scores, such as CLIF sequential organ failure assessment (CLIF-SOFA) score, CLIF consortium organ failure score (CLIF-C OFs), Model for End-stage Liver disease score (MELDs), MELD-Na score (MELD-Nas), and Child-Turcotte-Pugh score (CTPs) for predicting 28-day mortality (all P>0.05). However, the AUROC value of AARC ACLF score for predicting 90-day mortality was significantly lower than CLIF-C OFs, MELDs, MELD-Nas, and CTPs (all P<0.05), except CLIF-SOFA (P=0.076). In the patients with ACLF according to either AARC or EASL-CLIF definition, the AUROC value of AARC ACLF score was the lowest. However, there was no significant difference in predicting 28-day and 90-day mortality between AARC ACLFs and other scores. Lactate-free AARC ACLF score showed significantly higher accuracy in predicting 90-day mortality in total patients (P=0.014). However, the lactate-free AARC ACLFs showed similar AUROC values in predicting 28-day mortality in total patients and, predicting 28-day and 90-day mortality in ACLF patients.

Conclusions: AARC ACLF score showed comparable accuracy in predicting short-term mortality compared to other ACLF scores. Lactate-free ACLFs was also an excellent prognostic score in predicting short-term mortality.

Keywords: Acute-on-chronic liver failure, Validation, APASL

O-081

Empirical Carbapenem Treatment for Spontaneous Bacterial Peritonitis Reduced in-Hospital Mortality in Cirrhotic Patients with High CLIF-SOFA Score

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Aims: The third-generation cephalosporins (TGCs) has been recommended as the first-line empirical antibiotics for spontaneous bacterial peritonitis (SBP). However, recent European studies reported that antibiotics with broad spectrum may be necessary, especially for nosocomial SBP. In this study, we aimed to evaluate whether current treatment strategy for SBP is still valid in Korea, where the resistance to antibiotics prevails.

Methods: This study retrospectively involved consecutive SBP patients between September 2012 and January 2018 at a tertiary referral center in Korea. Primary endpoint was in-hospital mortality.

Results: A total of 287 patients with SBP were included: 110 patients (38.3%) were culture-positive. Among culture-positive SBP patients, 38 (34.5%) revealed third-generation cephalosporin (TGC)-resistant organisms. In entire SBP patients, the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score was associated with TGC-resistant organisms (adjusted odds ratio [aOR], 1.32; 95% confidence interval [CI], 1.14–1.54; P<0.001), whereas nosocomial infection was not (aOR, 1.16; 95% CI, 0.56–2.43; P=0.68). As initial empirical antibiotics, 207 patients (71.9%) received the TGCs and 58 (20.2%) received carbapenem. In entire SBP patients, an empirical TGC treatment was not associated with higher risk of in-hospital mortality than carbapenem treatment (aOR, 1.58; 95% CI, 0.74–3.39; P=0.24) if antibiotics regimens were adjusted according to clinical response or culture results. However, in a subgroup with high CLIF-SOFA score (≥7), TGCs as empirical antibiotics was an independent risk factor for higher in-hospital mortality (vs. carbapenem: aOR, 4.00; 95% CI, 1.14–14.03; P=0.03) after adjustment for CLIF-SOFA score, presence of hepatocellular carcinoma beyond Milan criteria, and nosocomial infection (see Table).

Table. Prognostic factors of In-hospital and 3 month-mortality among patients with high CLIF-SOFA score (≥7) (N=78)

Variable	In-hospital mortality		3-month mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
TGC treatment group	4.00 (1.14–14.03)	0.03	4.57 (1.18–17.76)	0.03
CLIF-SOFA score	1.98 (1.23–3.18)	0.005	1.88 (1.05–3.37)	0.03
HCC beyond Milan criteria	3.69 (1.20–11.33)	0.02	2.18 (0.64–7.35)	0.21
Nosocomial infection	0.62 (0.20–1.99)	0.43	1.07 (0.29–3.98)	0.92

Conclusions: TGCs still seem viable empirical antibiotics for SBP

patients. However, for patients with more severe organ dysfunction, empirical treatment with carbapenem might be more beneficial. A prospective multicenter study comparing carbapenem vs TGCs in this subgroup is warranted.

Keywords: Spontaneous bacterial peritonitis, Carbapenem, Third-generation cephalosporins

O-082

Estimating Renal Function and Predicting Prognosis of Patients with Decompensated Cirrhosis Using Serum and Urine Markers: Multicenter Prospective Observational Study

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Aims: This prospective observational study was performed to evaluate the best serum and urine markers for the assessment of renal function and predicting prognosis in patients with decompensated liver cirrhosis.

Methods: Hospitalized patients with decompensated liver cirrhosis were included. Laboratory tests including serum creatinine and cystatin C levels and urine N-acetyl-beta-D glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) levels were measured at the time of hospitalization.

Results: Three-hundred twenty-eight patients with decompensated cirrhosis were included. Age was 57.2±12.0 years and 237 patients (72.3%) were men. Alcoholic liver disease was the most frequent underlying liver disease (223 patients, 68.0%). Acute kidney injury (AKI) was combined in 41 patients (12.5%) at baseline. INR, serum creatinine and cystatin C levels, and urine NAG and NGAL levels were significantly higher in patients with AKI. During hospitalization, AKI was progressed in 37 patients (11.3%). In 287 patients without AKI, the incidences of AKI at 3, 6, 9, and 12 months were 15.4%, 22.2%, 28.6%, and 32.5%, respectively. On multivariate analysis, serum cystatin C and urine NAG levels were independent predictors of AKI. The optimal cutoff values of serum cystatin C and urine NAG levels were 1.055 mg/L (sensitivity 72.1%, specificity 59.1%) and 23.1 U/g urinary Cr (sensitivity 65.1%, specificity 70.0%), respectively. When patients were classified into 3 groups with these cutoff values of serum cystatin C and urine NAG levels (group 1, both low; group 2, one of two high; and group 3, both high), progression of AKI during hospitalization (P=0.001), incidence of AKI in patients without AKI at baseline (P=0.001), and mortality rate (P<0.001) differed significantly according to the serum cystatin C and urine NAG levels.

Conclusions: Serum cystatin C and urine NAG levels were useful markers for the assessment of renal function and predicting prognosis in patients with decompensated liver cirrhosis.

Keywords: Decompensation, Cirrhosis, Kidney injury, Cystatin C, N-acetyl-beta-D glucosaminidase

O-083

The Correlation between Spleen Stiffness and Portal Hypertension in Patients with Liver Cirrhosis

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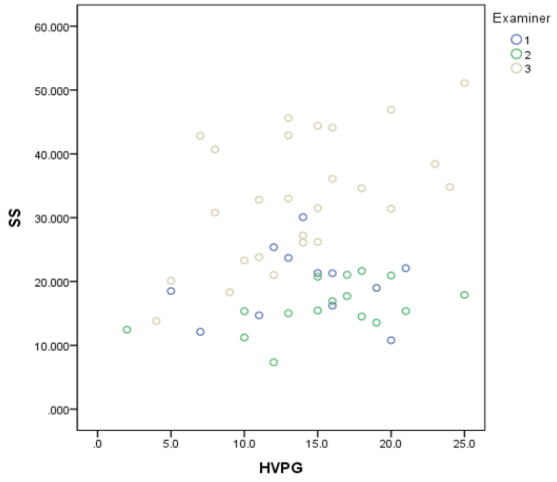
Aims: The most accurate way to determine degree of portal hypertension is the measurement of hepatic venous wedge pressure (HVPG). Since it is invasive and generally difficult to measure on routine clinical practice, there are many attempts to predict portal pressure by non-invasive method. We evaluate the usefulness of spleen stiffness (SS) assessed by 2-dimensional shear wave elastography (2D-SWE) for predicting HVPG.

Methods: From June 2017 to April 2019, 87 patients who measured SS and HVPG simultaneously were enrolled. Thirty four patients who showed invalid measurement (n=31) and combined hematologic malignancy (n=3) were excluded. Spleen stiffness was measured by 3 examiner using 2D-SWE (LOGIQ E9, GE healthcare) from two tertiary medical center.



Results: Fifty four patients were eligible for analysis. Most common etiology was alcoholic hepatitis (59.3%) and followed by chronic hepatitis B (18.5%). Patients consisted of Child-Pugh class A (n=6), B (n=37), C (n=11). The mean value of HVPG was

14.3±0.7 mmHg. The HVPG and SS did not showed correlation in entire cohort. (r=0.209, *P*=0.130). However, the subgroup analysis according to each examiner showed that SS from examiner 2 (n=16) and examiner 3 (n=26) showed significant correlation with HVPG, respectively (r=0.497, *P*=0.050 and r=0.531, *P*=0.005).

Conclusions: Whether SS is associated with HVPG is unclear. Standardization of measurement methods to reduce the inter-observer difference should be implemented and re-evaluation is need thereafter.

Keywords: Spleen stiffness, 2D-SWE, HVPG, Portal hypertension

O-084

Clinical Characteristics of Portal Hypertension in Korean Patients with Myeloproliferative Neoplasms

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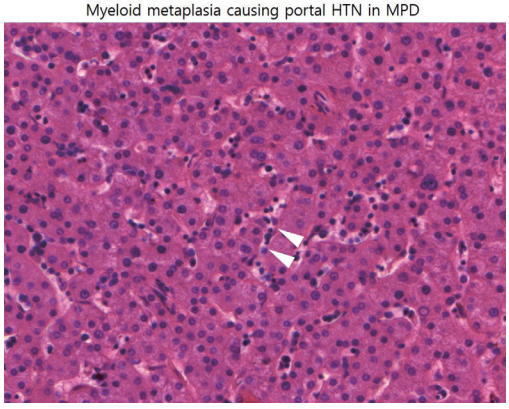
Aims: The Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), which include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), share many common clinical and molecular characteristics, including increased risk of thrombosis. Pathogenesis of portal hypertension (PHT) in MPN was previously shown to be correlated with degree of hepatic myeloid metaplasia and fibrosis, in addition to a major pre-hepatic component from increased splanchnic venous inflow. In this study, we investigated the clinical characteristics of PHT measured as gastroesophageal varices in Korean patients with MPNs.

Methods: From Jan. 2009 to Dec 2018, 1052 patients were newly diagnosed as MPNs including PV, ET, PMF, and MPN-unclassifiable (MPN-U). Among them, 228 patients underwent contrast-enhanced abdominal imaging study, which comprised our study cohort. We retrospectively reviewed medical records of the patients in the study cohort.

Results: In the study cohort, 11 patients (5%) had PHT demonstrated by gastroesophageal varix. Among patients with PHT, five patients had PV, 2 patients had ET, 3 patients had PMF, and 1 patient had MPN-U. Median age was 60 years old and 5 patients were male. Among them, three patients had portal vein thrombosis without protein C or S deficiency. Despite the gastroesophageal varices, liver function was normal with Child Pugh score 5 in every patient with PHT. Three patients had variceal bleeding, which had not been lethal and controlled by endoscopic ligation. All the patients (100%) with PHT had JAK2 V617F mutation, but only 119 / 217 patients (55%) without PHT had JAK2 V617F mutation (*P*<0.003). Seven patients received hydroxyurea and two patients received ruxolitinib treatment, but both of the medication resulted in no changes in variceal size by CT imaging. Living donor liver transplantation was performed in one patient with recurrent esophageal and gastric variceal bleeding, and explant pathology showed diffuse myeloid metaplasia in whole liver without fibrosis.

Myeloid metaplasia causing portal HTN in MPD



Conclusions: PHT in MPNs can be caused by hepatic myeloid metaplasia and result in the occurrence of gastroesophageal varix. JAK2 V617F mutation may be associated with the pathogenesis of the PHT in MPNs.

Keywords: Myeloproliferative neoplasm, Portal hypertension, JAK2V617F

14. Liver Cancer,Clinical

O-085

A Significant Diagnostic Role for Discrimination of Malignancy of Contrast Enhanced Ultrasound for Portal Vein Thrombosis in HCC Patients

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Aims: The characterization of portal vein thrombosis (PVT) as malignant versus bland is of great significance for therapeutic strategy in the patients with hepatocellular carcinoma (HCC). The aim is to investigate quantitative time-intensity curve (TIC) parameters and qualitative CEUS characteristics for differentiation between benign and malignant PVT, compared to the diffusion-weighted MRI (DWI).

Methods: A total of 50 HCC patients who showed the PVT in liver dynamic CT or MRI were consecutively enrolled and performed CEUS. TIC parameters were analyzed and DWI was performed using b values of 0, 400 and 800 sec/mm^2 at 3-T unit. A thrombus

was diagnosed as malignancy if it was enhanced on MRI.

Results: There were 19 bland thrombi and 31 malignant thrombi in 50 patients as the diagnostic enhancement of MRI. All qualitative parameters of CEUS such as arterial-phase enhancement, washout in the venous phase, vessel occlusion and expansion were significantly more common in malignant thrombosis than benign thrombosis (*P*<0.05). Regard to quantitative parameters of CEUS, shortened time to maximum enhancement, increased area under the TIC, prolonged time between the half amplitude values in each side of the maximum, prolonged the time from injection until the peak of enhancement in malignant thrombosis, were seen compared to benign thrombosis. These parameters were correlated with tumor stage and PIVKA II (*P*<0.05). A strong correlation was found between DWI-MRI and CEUS (*P*<0.0001). After an additional CEUS evaluation, 3 patients with the enhancement PVT on MRI were considered bland thrombus, in contrast, 4 patients with no enhancement PVT on MRI were considered malignant thrombus. Overall follow-up period, 5 of 7 patients consistent with the diagnosis of CEUS.

Conclusions: The present study showed that CEUS is comparable high diagnostic accuracy to DWI-MRI. Some TIC parameters by CEUS are useful for characterization of PVT in the patients with HCC.

Keywords: Contrast enhnaced ultrasonography, Portal vein thrombosis, Hepatocellular carcinoma

O-086

Comparison between Stereotactic Body Radiotherapy and Radiofrequency Ablation as First Therapy for Small Hepatocellular Carcinoma

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Background/Aim: Resection or ablative therapy is not indicated for many patients with hepatocellular carcinoma (HCC) because of advanced cirrhosis or tumor location. Stereotactic body radiotherapy (SBRT) may be an alternative treatment for these patients. This study compared the therapeutic effects of radiofrequency ablation (RFA) and SBRT in patients with small (3 cm) HCC.

Methods: Data of HCC patients who underwent SBRT or RFA as an initial treatment at two tertiary referral hospitals between March 2011 and February 2017 were reviewed. The patient inclusion criteria were a single nodule measuring ≤3 cm in size and not suitable for resection.

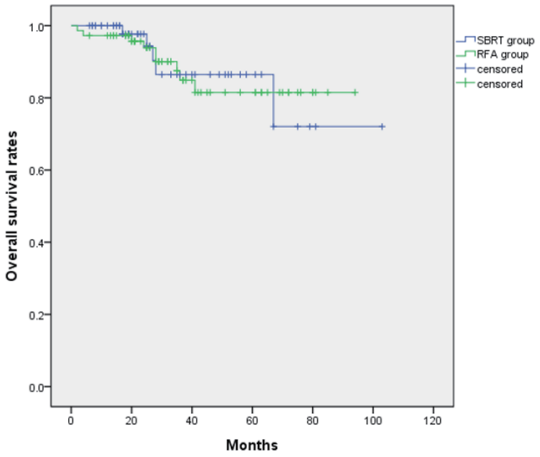
Table 1. Baseline characteristics

	SBRT (n = 57)	RFA (n = 73)	P-value
Age (years)	63.6 ± 10.1	60.3 ± 10.5	0.072
Sex (male/female)	36/21	51/22	0.420
Etiology			0.981
Alcoholic	13	18	
HBV	34	41	
HCV	8	6	
Others	6	4	
Liver cirrhosis Y/N	53/4	65/8	0.441
Child-Pugh score	5.47 ± 0.78	5.42 ± 0.79	0.049
Baseline total bilirubin level (mg/dL)	0.93 ± 0.53	0.82 ± 0.55	0.293
Baseline serum albumin level (g/L)	3.85 ± 0.55	3.90 ± 0.53	0.644
Platelet count (105/mm^3) (SD)	135.7 ± 81.5	133.7 ± 58.3	0.879
Baseline ALT level (IU/L)	26.2 ± 17.8	32.2 ± 39.9	0.292
Tumor size	1.69 ± 0.65	1.66 ± 0.46	0.710
AFP (median, IQR)	3.94 (2.64-20.78)	6.3 (2.96-19.40)	0.359

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP; alpha-fetoprotein; ALT, alanine aminotransferase; SD, standard deviation; IQR, interquartile range.

Table 2. Incidence of liver toxicity

	SBRT group (n = 57)	RFA Group (n= 73)	P-value
Grade ≥3 liver toxicity	5 (8.8%)	2 (2.7%)	0.131

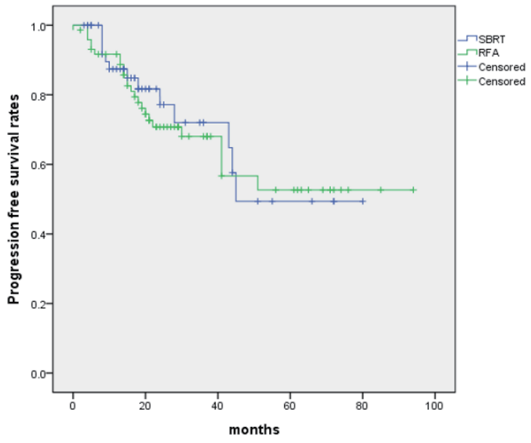


P = 0.960

Figure 1. Overall survival of all patients in the SBRT and RFA groups.

Results: SBRT and RFA were performed in 57 (SBRT group) and 73 (RFA group) patients, respectively. In the SBRT group, 21 patients received SBRT only and 36 received SBRT combined with transarterial chemoembolization (TACE). The one-, three- and five-year overall survival rates were 97.7%, 86.4%, and 72.0%, respectively, in the SBRT group compared with 97.3%, 87.5%, and 81.5%, respectively, in the RFA group, with no significant difference between the two groups (*P*=0.960). The estimated one-, three- and five-year progression-free survival rates were 87.4%, 64.8% and 49.4%, respectively, in the SBRT group and 84.8%, 70.8 and 52.6%, respectively, in the RFA group (P=0.712). Liver toxicity after treatment did not differ significantly between the SBRT (8.8%, 5/57) and RFA (2.7%, 2/71)

groups (P=0.131).



P = 0.712

Figure 2. Progression-free survival of all patients in the SBRT and RFA groups.

Conclusion: SBRT is an effective and safe treatment method for small HCCs, with survival and tumor recurrence rates similar to those of RFA.

Keywords: Hepatocellular carcinoma, Stereotactic body radiotherapy, Radiofrequency ablation, Survival rate

O-087

Prognostic Factors for Survival in Patients with Hepatocellular Carcinoma Treated by Trans-Arterial Radioembolization

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Aims: Trans-arterial radioembolization (TARE) is a form of radiation therapy performed by selective intra-arterial injection of microspheres loaded with Yttrium-90. TARE is known to be effective in the management of unresectable hepatocellular carcinoma (HCC). The aim of this study is to identify prognostic factors for overall survival (OS) and time to progression (TTP) in patients with HCC undergoing TARE.

Methods: This study included 73 consecutive HCC patients who underwent TARE from Jul 2009 to Jan 2018. The tumor responses to TARE were assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Results: The patients' baseline characteristics were as follows; median age was 66 years, 74% of male. The median tumor size was 9cm and 41% of the patients had tumors larger than 10 cm. Multifocal HCCs identified in 58% and 26% of the patients showed infiltrative tumor. 63% of the patients did not have portal vein tumor thrombus (PVTT), 10% had VP 1-2, and 27% had VP 3-4 of PVTT. Among 73 patients, 5 (7%) obtained complete response and 25 (34%) showed partial response at 3 months after TARE. Median OS was 27.6 months and TTP was 3.2 months. Multivariate analysis revealed that the absence of PVTT (hazard ratio [HR], 0.137; 95% confidence interval [CI], 0.057-0.331, *P*<0.001) was independent factor for OS. The absence of PVTT (HR, 0.330; 95% CI, 0.172-0.632, *P*=0.001) and tumor diameter ≤10 cm (HR, 0.287; 95% CI 0.135-0.611, *P*=0.001) were independent prognostic factors for TTP. Subgroup analysis of 46 patients without PVTT showed that the age ≤65 (HR, 0.240; 95% CI, 0.066-0.869, *P*=0.030), and single number of tumor (HR, 0.015; 95% CI, 0.092-0.771, *P*=0.015) were identified as independent factors with improved OS.

Conclusions: TARE is an effective therapy for patients with advanced HCC. Absence of PVTT before TARE is an independent predictive factor for both OS and TTP.

Keywords: Hepatocellular carcinoma, Portal vein tumor thrombus, Transarterial radioembolization

Keywords: Hepatocellular carcinoma, Portal vein tumor thrombus, Transarterial radioembolization

O-088

Prediction of Overall Survival after Resection or Radiofrequency Ablation Using Surrogates for Clinically Significant Portal Hypertension in Patients with Early Hepatocellular Carcinoma

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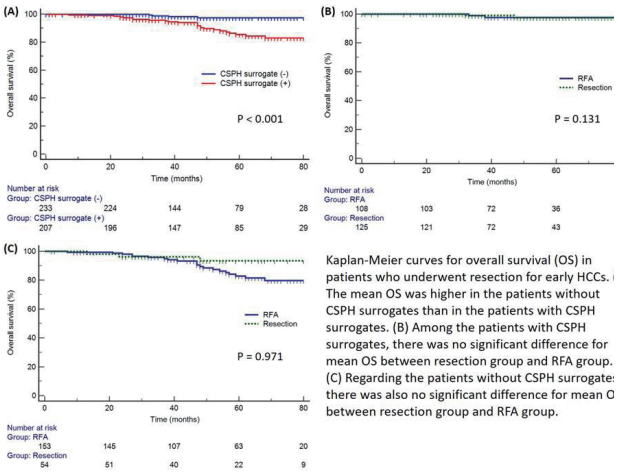
Aims: To evaluate the role of clinically significant portal hypertension (CSPH) surrogates in the prediction of prognosis and to compare the outcome of resection and radiofrequency ablation (RFA) according to the presence of surrogates for CSPH in patients with early hepatocellular carcinoma (HCC).

Methods: In this IRB-approved, single institutional study, we retrospectively enrolled 441 patients who underwent multidetector computed tomography (CT) and underwent first-line resection or RFA for single HCC ≤ 3 cm in diameter between January 2011 and December 2016. Upper endoscopy was performed in 211 patients. Surrogates for the presence of CSPH were considered present when at least one of the followings are present: gastroesophageal varices on upper endoscopy, thrombocytopenia (platelet count < 100 K/mm^3) with splenomegaly (spleen size > 12 cm), or varices on CT. Overall survival (OS) was assessed between the treatment methods and between the patients with or without CSPH surrogates using Kaplan Meier method.

Results: The mean and median follow-up period were 52.9 ± 21.6 months and 52.0 months (0–96 months, range), respec-

tively. The mean OS was higher in the patients without CSPH surrogates than in the patients with CSPH surrogates (93.6 months versus 87.3 months, *P*<0.001). Among the patients with CSPH surrogates, there was no significant difference for mean OS between resection group and RFA group (90.8 months versus 85.9 months, *P*=0.131). Regarding the patients without CSPH surrogates, there was also no significant difference for mean OS between resection group and RFA group (93.6 months versus 93.7 months, *P*=0.971).

Conclusions: The CSPH surrogates including varices on CT is associated with poorer OS in patients with single HCC ≤ 3 cm. There was no significant difference for OS between resection group and RFA group among the patients with or without CSPH surrogates.



Kaplan-Meier curves for overall survival (OS) in patients who underwent resection for early HCCs. The mean OS was higher in the patients without CSPH surrogates than in the patients with CSPH surrogates. (B) Among the patients with CSPH surrogates, there was no significant difference for mean OS between resection group and RFA group. (C) Regarding the patients without CSPH surrogates there was also no significant difference for mean O between resection group and RFA group.

Keywords: Hepatocellular carcinoma, Portal hypertension, Prognosis, Resection, Radiofrequency ablation

O-089

Clinical Significance of the Thioredoxin System and Thioredoxin Domain Containing Protein Family in Hepatocellular Carcinoma

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Aims: Oxidative stress occurs due to the excessive generation of cellular reactive oxygen species and antioxidant system dysfunction. The thioredoxin (TXN) system and TXN-domain-containing protein (TXNDC) family form networks maintaining the cellular reducing environment. Recently, the importance of these genes in the tumor environment has been emphasized. Therefore, we investigate the clinical significance of TXNs and TXNDC family members in HCC.

Methods: Genomic data from 367 hepatocellular carcinoma (HCC) patients who underwent hepatic resections were analyzed to determine genetic alterations in mRNA and protein levels between patients and healthy controls. In addition, functional enrichment and survival analyses were performed.

Results: HCC patients were shown to have the enhanced expression of TXN, TXNRD1, TXNDC7/9/14 mRNA and protein compared with that of controls. In accordance to the survival analyses, strong associations were found that patients with TXN, TXNRD1, and TXNDC1/7/9 alterations were proven to have poor prognosis in overall survival. Moreover, gene set enrichment analyses and network analyses revealed that positive correlations were found in mRNA expression of TXN, TXNRD1, and TXNDC7/9 genes with upregulation of the genes to tumor promoting genes, specifically mTORC1, E2F targets, and Myc targets. On the other hand, elevated expressions of TXNIP and TXNDC11 genes were correlated with suppression of the above tumor promoting genes.

Conclusions: TXN system and TXNDC family gene panel obtained from the resected tissue of the HCC patients could be used to predict survival prognosis of HCC and these genes could be considered as potential therapeutic targets for improving HCC survival.

Keywords: Thioredoxin, TXN-domain-containing protein, Hepatocellular carcinoma, Overall survival

O-090

Contrast-Enhanced Ultrasound with Perfluorobutane for Hepatocellular Carcinoma Surveillance: A Multicenter Diagnostic Trial (SCAN)

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Aims: Ultrasound has served as a standard surveillance tool for

hepatocellular carcinoma, while its detection rate and false referral rate are suboptimal. We aimed to evaluate the added value of contrast-enhanced ultrasound using perfluorobutane microbubble (Sonazoid) to conventional B-mode ultrasound as a hepatocellular carcinoma surveillance tool for patients with liver cirrhosis.

Methods: This prospective, multi-institution, diagnostic trial using an intra-individual comparison design in a single arm of patients was conducted at five referral hospitals. Patients having liver cirrhosis and undergoing ultrasound for hepatocellular carcinoma surveillance were eligible for the study. All patients underwent contrast-enhanced ultrasound (Kupffer-phase ± vascular-phase ultrasound) immediately following conventional B-mode ultrasound. The primary endpoints were the detection rate of early-stage hepatocellular carcinoma and the false referral rate.

Results: From October 2014 through August 2016, 524 patients (mean age ± standard deviation, 54 ± 9 years; 184 women) were enrolled. The detection rate of early-stage hepatocellular carcinoma was 0.6% (95% CI, 0.1%–1.7%; 3 of 524 patients) on B-mode ultrasound and 1.0% (95% CI, 0.3%–2.2%; 5 of 524 patient) on contrast-enhanced ultrasound, respectively. There was no statistically significant difference in the detection rate of early-stage hepatocellular carcinoma (*P*=0.16). The false referral rate was 4.6% (95% CI, 3.0%–6.7%; 24 of 524 patients) on B-mode ultrasound and 1.3% (95% CI, 0.5%–2.7%; 7 of 524 patients) on contrast-enhanced ultrasound, respectively. A statistically significant difference was observed for the false referral rate (*P*<0.001).

Conclusions: The use of perfluorobutane significantly reduced the false referral rate of B-mode US without significant improvement in detection rate.

Keywords: HCC, Surveillance, Ultrasound

15. Liver Cancer,Clinical

O-091

Reclassification of Microvascular Invasion in Hepatocellular Carcinoma According to Its Anatomical Location

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Aims: The most important factor for TNM stage in hepatocellular carcinoma (HCC) is microvascular invasion (MVI), which includes all vascular invasions detected in the microscopic examination. In this study, we classified microvascular invasion into microvessel invasion (MI) and microscopic portal vein invasion (MPVI) and evaluated their prognosis after curative resection of HCC.

Methods: From January 2009 to December 2015, 514 patients who underwent surgical resection without any preoperative treatments or gross vascular invasion were included. Among them, 241 patients (46.9%) were found to have MVI in the pathologic examination. The patients with MVI were divided into three groups: original MVI group (n=241), MI only group (n=195) and MPVI group (n=46). Clinicopathologic features were compared between MI only group and MPVI group and prognosis after resection was analyzed among the three groups.

Results: MPVI group showed larger tumor size (4.2 vs 3.8, *P*=0.001) and higher level of tumor markers (AFP, 3238 vs 2896, *P*=0.017 and PIVKA; 1602 vs 926, *P*=0.001) than MI only group. In survival analysis, 5-year DFS rate after resection were 47.1% (MI only group), 43.6% (original MVI group), and 27.8% (MPVI group) respectively (*P*=0.000). And 5 year-OS rate after resection of MI only group, original MVI group and MPVI group were 73.3%, 69.0%, and 48.6% respectively (*P*=0.000).

Conclusions: Patients with MPVI have showed more aggressive tumor characteristics than patients with MI only. Patients with MPVI showed the worst prognosis after resection among three groups. Therefore, the original MVI should be divided into MI and MPVI according to their anatomical location.

O-092

The Clinical Impact of Applying BCLC Guideline for the Treatment of Recurrent Intrahepatic Single and Small Sized Hepatocellular Carcinoma

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Aims: The long-term survival outcome of hepatocellular carcinoma (HCC) is unsatisfactory due to high recurrence rate. And majority of cases showed solitary intra hepatic recurrence. However, there is not an established treatment guideline for the recurrence. This study aimed to determine the survival benefit of treatment strategies according to Barcelona Clinic Liver Cancer stage (BCLC), especially in the patient with BCLC O at recurrence stage (reBCLC-O).

Methods: Study included patients with recurrence after primary hepatic resection at two centers in Korea, between 2005 and 2011. Among the patients, reBCLC-O who is defined as asymptomatic, single and less than 2cm sized in diameter intrahepatic HCC were selected. Survival outcomes of propensity score-matched groups were compared according to treatment modality (Curative and non-curative treatment).

Results: In 917 patients, 394 patients of reBCLC-O were selected. Among these, 150 underwent curative treatment and 203 had non-curative treatment. After propensity score matching, the two groups were well balanced (94 patients in each group). The 1-,3 and 5-year overall survival rates in the curative treatment group were 94,73 and 63 per cent, compared with 86,66

and 58 per cent in non-curative treatment group (*P*=0.236). In multivariable analysis, tumor size, number of tumor and albumin level at recurrence stage were independent predictors of worse overall survival.

Conclusions: Non-curative treatment (chemoembolization) can be an alternative treatment option associated favorable overall survival for the patients of reBCLC-O when curative treatment is not feasible.

O-093

Chronological Improvement in Long-Term Outcomes of Surgical Resection for Patients with Hepatocellular Carcinoma: Two Large-Volume Center Study

Yun Bin Lee[1], Jeong-Hoon Lee[1*], Hyo Young Lee[1], Cheol-Hyung Lee[1], Minseok Albert Kim[1], Heejoon Jang[1], Sun Woong Kim[1], Suk Kyun Hong[2], Eun Ju Cho[1], Su Jong Yu[1], Nam-Joon Yi[2], Kwang-Woong Lee[2], Jong Man Kim[3], Jae-Won Joh[3], Yoon Jun Kim[1], Kyung-Suk Suh[2], Jung-Hwan Yoon[1]

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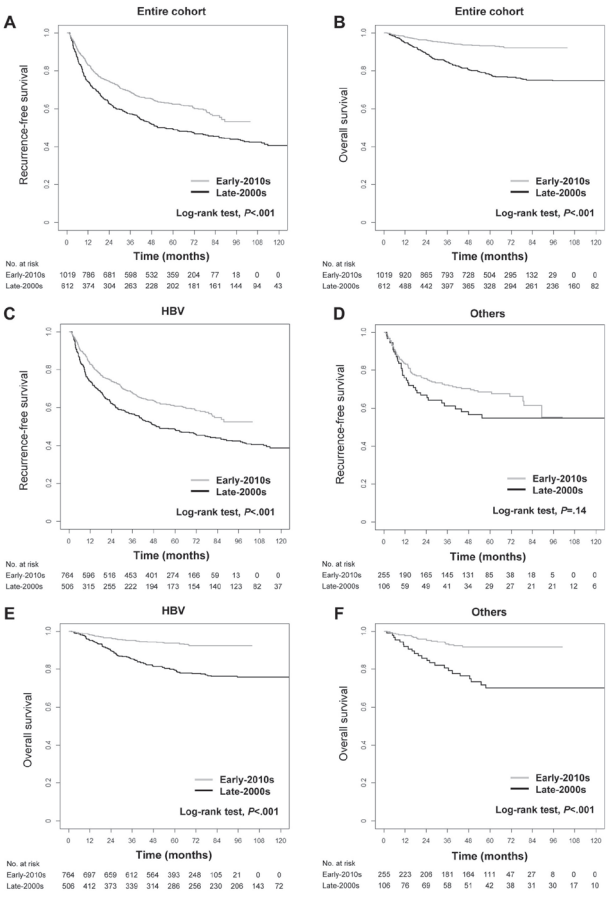
Aims: As the treatment for underlying liver diseases developed, clinical outcomes of patients with hepatocellular carcinoma (HCC) has been improved. We investigated whether long-term outcomes following surgical resection in HCC patients were changed over time according to the etiology of liver disease.

Methods: In this study, 1,631 consecutive patients who underwent surgical resection for HCC as an initial treatment between 2016 and 2013 at two large-volume centers in Korea (Seoul National University Hospital and Samsung Medical Center) were included. Study patients were divided into two groups by the year of operation: late-2000s (2006–2009: n=612) or early-2010s group (2010–2013: n=1,019). Primary and secondary endpoints were recurrence-free survival (RFS) and overall survival (OS), respectively.

Results: Median follow-up duration was 5.7 years in the late-2000s group and 5.0 years in the early-2010s group. Both RFS and OS were significantly longer in the early-2010s group among entire cohort (both log-rank *P*<0.001) (Fig. 1A–B). Multivariable Cox analyses revealed that the early-2010s group was an independent predictor of both prolonged RFS (adjusted hazard ratio [aHR]=0.69, 95% CI=0.58–0.81, *P*<0.001) and OS (aHR=0.30, 95% CI=0.22–0.41, *P*<0.001) compared to the late-2000s group. When patients were categorized into the two subgroups according to underlying liver disease (hepatitis B virus [HBV], n=1,270; and others, n=361), the aHR of RFS was similar between two subgroups (HBV subgroup: aHR=0.69, 95% CI=0.58–0.82, *P*<0.001; other subgroup: aHR=0.72, 95% CI=0.48–1.08, *P*=0.12) (Fig. 1C–D). OS of early-2010s group was also significantly improved in both subgroups (HBV subgroup: aHR=0.30, 95% CI=0.21–0.43, *P*<0.001; other subgroup: aHR=0.27, 95% CI=0.14–0.50, *P*<0.001) (Fig. 1E–F). HRs were maintained after balancing baseline characteristics using inverse probability weighting.

Figure 1



Conclusions: Long-term clinical outcomes of surgical resection for the treatment of HCC were improved over time with approximately 30% decreased risk of recurrence or death.

Keywords: HCC, Surgical resection, Etiology, HBV, RFS, OS, Liver cancer

O-094

Is Liver Resection Justified for Multinodular Hepatocellular Carcinoma in Patients with Cirrhosis? A Multicenter Analysis of 1,066 Patients

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Aims: The role of liver resection for multinodular (≥ 3 nodules) hepatocellular carcinoma (HCC) remains unclear, especially in patients with severe underlying liver disease. We aim to evaluate short-term and long-term outcomes in cirrhotic patients undergoing liver resection for multinodular HCC.

Methods: From a multicenter database, cirrhotic patients who underwent curative liver resection of HCC were enrolled and divided into two groups: the non-multinodular and multinodular HCC groups. Perioperative mortality and morbidity, and overall survival (OS) and recurrence-free survival (RFS) were compared between the two groups.

Results: Among 1,066 cirrhotic patients, 906 (85.0%) had single- or double-nodular HCC (the non-multinodular group), while 160 (15.0%) had multinodular HCC (the multinodular group). There were no any differences in postoperative 30-day mortality and morbidity between the two groups (1.8% vs. 1.9%, *P*=0.923, and 36.0% vs. 39.4%, *P*=0.411, respectively). However, the 5-year OS and RFS rates of the multinodular group were worse than those of the non-multinodular group (34.6% vs. 58.2%, and 24.7% vs. 44.5%, both *P*<0.001). Multivariable analyses revealed that tumor numbers ≥ 5, total tumor diameter ≥ 8 cm and microvascular invasion were independent risk factors for decreased OS and RFS after resection of multinodular HCC in cirrhotic patients.

Conclusions: Liver resection could be safely performed for multinodular HCC in patients with cirrhosis, with an overall 5-year survival rate of 34.6%. Tumor number ≥ 5, total tumor diameter ≥ 8 cm and microvascular invasion were independently associated with decreased OS and RFS after resection in cirrhotic patients with multinodular HCC.

O-095

Change in the Recurrence Pattern and Risk Factors over Time after the Complete Cure of Hepatocellular Carcinoma: Ten-Year Follow-Up Study

Han Ah Lee[1], Seung Up Kim[2], Hyun Gil Goh[1], Tae Hyung Kim[1], Sun Young Yim[1], Young-Sun Lee[1], Sang Jun Suh[1], Young Kul Jung[1], Ji Hoon Kim[1], Yeon Seok Seo[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Kwan Soo Byun[1], Soon Ho Um[1]

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Aims: Recurrence pattern and risk factors for recurrence after complete cure of hepatocellular carcinoma (HCC) changes over time. However, there were only few studies evaluated the recurrence of HCC in time-dependent analysis.

Methods: All patients with first diagnosed Barcelona-Clinic Liver Cancer (BCLC) stage A HCC which were completely cured with surgical resection or radiofrequency ablation (RFA) at Korea University Hospital and Yonsei University Severance Hospital were included between 2007 and 2016.

Results: In total, 1,496 patients who were cured from BCLC stage A HCC with surgical resection or RFA were included. Liver cirrhosis was combined in 919 patients (61.4%). Type of treatment was surgical resection in 991 patients (63.5%) and RFA in 570 patients (36.5%). The change of recurrence pattern over time is presented in Figure 1. Patient population and risk factors for HCC recurrence also changed with the time progression. In patients without HCC recurrence within 1 year, combined liver cirrhosis, treated with RFA, number and size of tumors, and MELD score were the independent risk factors for HCC recurrence at 1 year after treatment for HCC. While, in patients without HCC recurrence within 3 years, age, combined liver cirrhosis, and treated with RFA were the independent risk factors for HCC recurrence at 3 years after treatment for HCC. Combined cirrhosis and treatment type were two independent risk factors for HCC recurrence in almost time points. When patients were classified into four groups according to the presence of liver cirrhosis and the type of treatment, the cumulative incidences of HCC recurrence decreased with time progression in all groups, but the recurrence rate at the same time point was significantly different between groups.

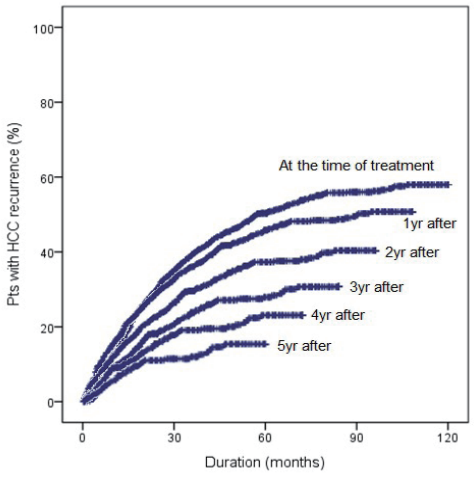

Figure 1. The cumulative incidence of HCC recureence at the time of resection or RFA, and at 1, 2, 3, 4, and 5 years after resection or RFA.

Conclusions: Recurrence pattern and risk factors for recurrence after complete cure of HCC changes with time progression. Appropriate surveillance strategy at each time point is needed.

Keywords: Recurrence, Hepatocellular carcinoma, Cirrhosis, Surveillance strategy

O-096

Surgical Resection Should Be Considered in Resectable Solitary Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis of Patients with Child A

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Aims: Surgical resection and locoregional therapies such as combination transarterial chemoembolization (TACE) and/or radiation therapy (RT) are commonly used in those patients. The aim of present study is to compare the outcomes between surgical resection and combination therapy included TACE and RT in resectable solitary HCC with PVTT.

Methods: We prospectively enrolled in resectable solitary HCC with PVTT between 2010 and 2015. Resectability was defined by three experienced surgeons. Patients were selected using propensity score matching.

Results: All patients were Child-Pugh class A and ECOG performance grade ≤1. Forty-four patients underwent surgical liver resection (SR group) and 72 patients received combination therapies (Combination group). Age, AFP, PIVKA-II, and tumor size were significantly different between the two groups. Therefore, propensity score matching used four variables. Thirty-five patients in the SR group and 45 patients in the combination group were selected after propensity score matching. The 1-year, 2-year, and 3-year patient survival rates were 85.7%, 71.3%, and 68.2% in the SR group and 68.9%, 53.2%, and 38.1% in the combination group (P=0.008). Multivariate analysis showed that surgical resection, low platelet counts, and male are closely associated patient survival in solitary HCC with PVTT.

Conclusions: Surgical resection may improve patient survival in solitary resectable HCC wih PVTT patients. Surgical liver resection is always considered as curative treatment in solitary resectable HCC with PVTT in patients with Child A.

16. Basic & Others

O-097

Serine Protease HtrA2/Omi Deficiency Impairs Mitochondrial Homeostasis and Promotes Liver Fibrosis

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Aims: The loss of mitochondrial function impairs intracellular energy production and potentially results in chronic liver disease. Increasing evidence suggests that mitochondrial dysfunction in hepatocytes contributes to the activation of hepatic stellate cells, thereby resulting in hepatic fibrogenesis. High-temperature requirement protein A2 (HtrA2/Omi), a mitochondrial serine protease, is responsible for quality control in mitochondrial homeostasis. However, little information is available regarding its role in mitochondrial damage during the development of liver fibrosis. This study investigated whether HtrA2/Omi regulates mitochondrial function during the development of liver fibrosis.

Methods: HtrA2/Omi expression was analyzed in liver tissues from mice model of the carbon tetrachloride (CCl4)-induced liver fibrosis and from patients with liver cirrhosis. We silenced HtrA2/Omi expression in FL83B hepatocytes with RNA interference. Hepatocytes were isolated from motor neuron degeneration 2 (mnd2)-mutant mice harboring the missense mutation Ser276Cys in the protease domain of HtrA2/Omi. For study of mitochondrial morphology and function, hepatocyte and liver tissue were analyzed by transmission electron microscopy, quantitative polymerase chain reaction, and immunoblots.

Results: HtrA2/Omi expression considerably decreased in human and mouse fibrotic liver tissues. HtrA2/Omi knockdown in hepatocytes induced the accumulation of damaged mitochondria and provoked oxidative stress. Moreover, we found that mnd2-mutant mice altered mitochondrial morphology and function, which increased oxidative stress and promoted liver fibrosis. Conversely, the overexpression of HtrA2/Omi via hydrodynamics-based gene transfer led to the antifibrotic effects in CCl4-induced liver fibrosis mice model through decreasing collagen accumulation and enhancing anti-oxidative activity by modulating mitochondrial homeostasis in the liver.

Conclusions: These results suggest that suppressing HtrA2/Omi expression promotes hepatic fibrogenesis via modulating mitochondrial ROS generation, and these novel mechanistic insights involving the regulation of mitochondrial homeostasis by HtrA2/Omi may be of importance for developing new therapeutic strategies for hepatic fibrosis.

Supported by grants of the Basic Science Research Program through NRF-2016R1D1A1B03931395.

Keywords: Mitochondrial function, Hepatic fibrogenesis, HtrA2/Omi, Reactive oxygen species stress, Mitochondrial homeostasis

O-098

Glutamate/mGluR5 Signaling in Stellate Cells Drives Endocannabinoid-Mediated Alcoholic Steatosis

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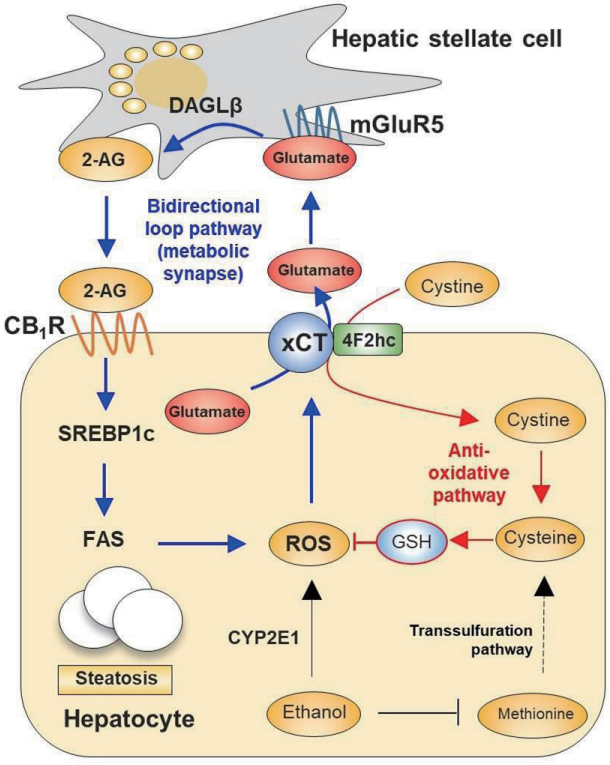
Aims: Paracrine activation of hepatic cannabinoid receptor 1 (CB1R) by hepatic stellate cell (HSC)-derived 2-arachidnoylglycerol (2-AG) is one of the critical mechanisms mediating alcoholic steatosis by stimulating *de novo* lipogenesis in hepatocytes. However, the precise mechanism of 2-AG production in HSCs is unknown.

Methods: Levels of plasma glutamate were measured in the samples from 33 patients with biopsy-proven alcoholic liver disease and 4 healthy individuals (controls). To examine alcohol-induced glutamate excretion, endocannabinoid production and consequent steatosis, C57BL/6 wild type, global metabotropic glutamate receptor 5 (mGluR5) knockout and hepatocyte-specific xCT knockout mice were fed liquid ethanol diet for 8 weeks. In addition, mGluR5 specific antagonist or xCT inhibitor was treated to ethanol-fed mice to test their therapeutic potentials. For *in vitro* experiments, freshly isolated primary HSCs and hepatocytes were used. RNA sequencing, histology, immunoblots, quantitative polymerase chain reaction, and metabolite measurements were performed.



Results: We found that chronic alcohol consumption induced hepatic cysteine deficiency and subsequent glutathione depletion by impaired transsulfuration pathway. A compensatory increase in hepatic cystine-glutamate antiporter xCT resulted in significant increase of extracellular glutamate levels coupled to cystine uptake both in mice and in patients. Alcohol also induced the selective expression of mGluR5 in HSCs, and mGluR5 activation stimulated 2-AG production in HSCs. Consistently, genetic or pharmacologic inhibition of mGluR5 or xCT attenuated alcoholic steatosis in mice via suppression of 2-AG production and subsequent CB1R-mediated de novo lipogenesis.

Conclusions: Our findings propose that a similar bidirectional signaling operates at a metabolic synapse between hepatocytes and HSCs through xCT-mediated glutamate/mGluR5 signaling to produce 2-AG, which induces CB1R-mediated alcoholic steatosis. This novel pathway could be a potential theragnostic target for alcoholic liver disease.

Keywords: Alcoholic fatty liver disease, Hepatic stellate cells, Endocannabinoid, Transsulfuration pathway

O-099

Src Inhibition Attenuates Liver Fibrosis by Downregulating CTGF and Phospho-Smad3

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Aims: The SRC kinase family comprises non-receptor tyrosine kinases that are ubiquitously expressed in all cell types. Active Src phosphorylates and thereby activates various signaling proteins such as signal transducer and activator of transcription 3, AKT, and epidermal growth factor receptor, which regulate various biological activities. Although Src is reportedly activated in pulmonary and renal fibrosis, little is known about its role in liver fibrosis. This study investigated whether inhibition of Src protects against liver fibrosis.

Methods: Liver fibrosis was induced by thioacetamide (TAA)-injection for 8 weeks in C57BL/6 mice and saracatinib was administered orally premixed with the pellet. We cultured AML12, LX2 and mouse primary hepatocytes. The effect of saracatinib on liver fibrosis was determined by Sirius red, immunohistorchemistry, real-time RT PCR and western blot analysis.

Results: Expression of SRC was upregulated at the mRNA and protein levels in liver of TAA-injected mice. In addition, we confirmed that phosphorylation of SRC was increased in TAA-injection mice. The Src inhibitor saracatinib reduced TAA-induced collagen, αSMA and CTGF expression. *In vitro* studies also showed that TGF-ß induces SRC phosphorylation and saracatinib inhibited TGF-ß-stimulated CTGF and PAI-1 expression. In addition, saracatinib inhibited TGF-ß-stimulated phospho-Smad3.

Conclusions: This study shows that Src is involved in TAA-induced liver fibrosis. Src inhibitors attenuated TAA-induced liver fibrosis and TGF-ß-induced CTGF expression. Furthermore, the inhibitory effect of Src inhibitors on liver fibrosis was associated with attenuation of TGF-ß-induced phospho-Smad3 expression.
Keywords: Src kinase, Saracatinib, Liver fibrosis, CTGF

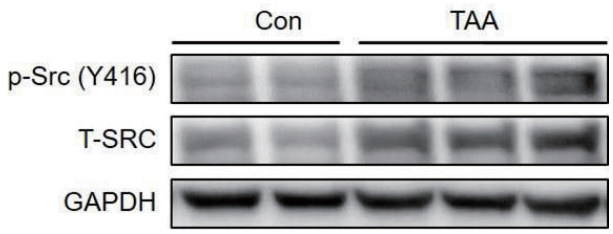

Figure 1.

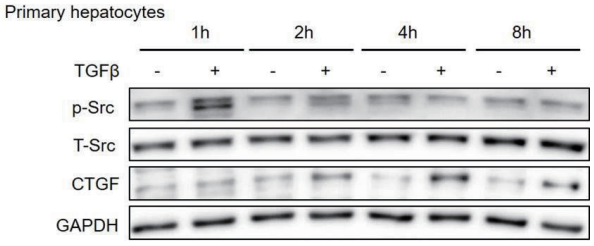

Figure 2.

Figure 3.

O-100

Correlation of Infiltration by T Cells and Macrophages with the Severity of Liver Damage in Drug-Induced Liver Injury: Implications in Responsiveness to Steroid Therapy

Hyun Yang[1,2], Pil Soo Sung[1,2], Kwon Yong Tak[1,3], Jae Jun Lee[1,2], Hee Chul Nam[1,3], Jeong Won Jang[1,3], Si Hyun Bae[1,2], Jong Young Choi[1,3], Seung Kew Yoon[1,3], Eun Sun Jung[4], Sang Wook Choi[1,2]

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Aims: Drug-induced liver injury (DILI) is liver injury caused by the interplay between drugs, their metabolites and host immune response. The aim of this study is to characterize liver infiltrating immune cells in DILI and to evaluate the correlation between infiltrating immune cells and clinical outcome.
Methods: From January 2017 to February 2019, 23 patients with DILI were prospectively enrolled in this study. Diagnosis of DILI was based on patient medication history after exclusion of other etiology (virus, alcohol, autoimmune, ischemic hepatitis or extrahepatic obstruction of the bile duct). Liver biopsy was performed, and immunohistochemical stain for CD3, CD68, CD20, and CD38 was done. Experienced pathologist confirmed the pathologic and immunohistochemical findings.
Results: The causes included "health foods or dietary supplements" (8, 34.8%), "folk remedies" (6, 26.1%), "medications" (4, 17.4%), "herb" (3, 13.0%), "combined" (2, 8.7%). 18 patients (78.3%) treated with steroid. Two patients progressed to hepatic failure and recovered after steroid treatment. All patients were completely recovered from DILI at one month after diagnosis, whether they were treated with steroid or not. The frequency of infiltrated T cells, macrophages, and B cells was quantified by immunohistochemistry. The amounts of T cells, showed linearly ascending correlation with total bilirubin (r=0.370, *P*=0.030) and MELD (model for end-stage liver disease) score (r=0.340, *P*=0.047). The amounts of macrophages, showed linearly ascending correlation with total bilirubin (r=0.401, *P*=0.020), AST (r=0.445, *P*=0.010), and MELD (model for end-stage liver disease) score (r=0.402, *P*=0.020). The amounts of activated T cells showed linearly ascending correlation with AST (r=0.475, *P*=0.048).
Conclusions: In this study, we found the positive correlation between the amounts of T cells and macrophages infiltrations and deterioration of liver function in DILI. Favorable responses to steroid therapy suggest that vigorous innate and adaptive immune responses play critical roles in DILI.
Keywords: Drug-induced liver injury, Steroids, Adaptive immunity, Innate immunity

O-101

Liver Enzyme Variability and the Risk of Heart Diseases and Mortality: A Nationwide Population-Based Study of 6.5 Million Subjects

Eun Ju Cho[1,§], Kyungdo Han[2,§], Dong Wook Shin[3,4,*], Su Jong Yu[1,*], Yunbin Lee[1], Jeong-Hoon Lee[1], Seung-Pyo Lee[5,6], Yoon Jun Kim[1], Jung-Hwan Yoon[1]

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Aims: Liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT), have been suggested as surrogate markers of various cardiovascular diseases. However, previous studies assessed liver enzymes only once at baseline, and the impact of variability of liver enzymes has not been examined. In this study, we investigated the association between liver enzyme variability and the risk of mortality and cardiovascular outcomes in the general population using nationally representative data.

Methods: A total of 6,496,271 subjects who participated ≥3 health examinations within 5 years from the index year (2009-2010) were included. Variability in ALT, AST, and GGT was measured using the variability independent of the mean. Multivariate Cox proportional hazards models were used.

Results: There were 106,413 deaths (1.6%), 53,385 MIs (0.8%), 65,143 AFs (1.0%), and 50,139 CHFs (0.7%) during a median follow-up of 6.0 years. In the multivariable analysis, there was increasing trends of the association between liver enzyme variability and all study outcomes. The degrees of association were largest for GGT variability. For the highest quartile of GGT variability relative to lowest one, the risk of all-cause mortality increased by 27% (hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.25–1.29), myocardial infarction by 8% (HR, 1.08; 95% CI, 1.06–1.11), atrial fibrillation by 24% (HR, 1.24; 95% CI, 1.18–1.31), and congestive heart failure by 22% (HR, 1.22; 95% CI, 1.19–1.25). These findings were consistent regardless of alcohol consumption, body mass index, and degree of fatty liver measured by fatty liver index. Sensitivity analysis excluding subjects with outcomes within the first 2 years of follow-up also revealed similar results.

Conclusions: Higher visit-to-visit variability of liver enzyme was an independent predictor of all-cause mortality and cardiovascular events.

Keywords: Variability, Liver enzyme, Mortality, Cardiovascular outcome

O-102

Increased Annual Incidence of Pyogenic Liver Abscess and Its Risk Factors: An Analysis from HIRA-NPS of South Korea, 2012–2016

Jeong-Ju Yoo[1*], Sang Gyune Kim[1], Young Seok Kim[1], Soung Won Jeong[2], Jae Young Jang[2], Sae Hwan Lee[3], Hong Soo Kim[3], Baek Gyu Jun[4], Young Don Kim[4], Gab Jin Cheon[4]

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Aims: The epidemiology of pyogenic liver abscess (PLA) continues to change but few population-based studies have been conducted in Korea. This study investigated the epidemiology and clinical outcomes of PLA patients in the current 5 years.

Methods: We used the Health Insurance Review and Assessment Service-National Patient Samples (HIRA-NPS) between 2012 and 2016. The HIRA-NPS, including approximately 1.4 million individuals, is a stratified random sample of 3% of the entire Korean population. The annual incidence rates, demographic data, underlying diseases, complications, and mortality rates were analyzed using the data.

Results: The annual incidence of PLA for all age groups increased gradually in Korea from 0.0273% (388 cases) in 2000 to 0.0298% (438 cases) in 2016. It occurred more commonly in the male sex, and older age (>65 years). Among the 2042 adult patients with PLA, 998 (48.9%) patients had diabetes mellitus, 108 (8%) patients colon cancer, and 346 (16.9%) patients biliary disease. Surgery due to PLA was in 44 (2.2%) patients, and 1 (0.05%) patient received enucleation due to endogenous endophthalmitis. The mortality rate was 8.2%. In particular, the mortality rate was 13.4% in patients aged over 65 and 19.3% over 85.

Conclusions: The incidence of PLA is increasing and the number of patients with comorbidity is also increasing. Especially, the mortality of PLA tends to increase in the old age. Further surveillance of epidemiology using National Health Insurance data is needed.

Keywords: Liver abscess, Epidemiology, Incidence, Mortality

The Liver Week 2019

June 20-22, 2019 | BEXCO, Busan, South Korea

Oral Poster Presentation

[Group 1] June 21, 2019 | 15:30-16:30

ALD & NAFLD

OP-001

Exosomal Double-Stranded RNA Promotes Interleukin-1β Production in Kupffer Cells via Toll-Like Receptor 3 in Alcoholic Liver Injury

Jun-Hee Lee[1], Young-Ri Shim[1], Wonhyo Seo[2], Won-Il Jeong[1], Myung-Ho Kim[1], Ye-eun Kim[1], Tom Ryu[1], Keungmo Yang[1]

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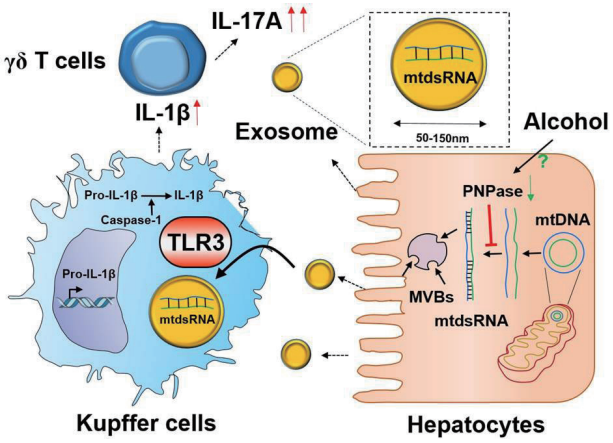
Aims: Damaged hepatocytes release extracellular vesicles (EVs) into nearby milleu by various stimuli including alcohol. During alcohol metabolism, mitochondrial damage occurs by CYP2E1-mediated ROS. A recent study reported the accumulation of mitochondrial double-stranded RNA (mtdsRNA) by inhibition of mitochondrial degradosome such as PNPase. However, It has not been reported the presence of mtdsRNA in hepatocytes and its effects on alcoholic liver disease. Here, we report alcohol increases hepatic mtdsRNA and delivered mtdsRNA via hepatic exosomes could be detected by TLR3 and promotes interleukin-1β in Kupffer cells.

Methods: ALD is induced by binge ethanol drinking in WT and TLR3 KO mice with or without Kupffer cell deletion by clodronate. To investigate the presence of mtdsRNA, immunofluorescent staining were performed. IL-17 producing cells were identified by flow cytometry. Using differential centrifugation of hepatic EVs, microvesicles and exosomes were investigated after ethanol treatment to primary hepatocytes. To identify the size of contents in EVs, Bioanalyzer analyses were done after RNA extraction from EVs by using TRIzol.

Results: After binge drinking, increased IL-17 was observed in γδ T cells of WT, but not in TLR3 KO mice. In addition, IL-17 production of γδ T cells was not changed by depletion of Kupffer cells, followed by decreased IL-1β expression after binge drinking. In qPCR and western blotting, level of PNPase was significantly decreased in the liver of ethanol-fed mice. In Bioanalyzer analyses, exosomes isolated ethanol-treated hepatocytes (EtOH-exosomes) contained much of small nucleotide RNA compared with control. After treatment with EtOH-exosomes into Kupffer cells, IL-1β expression was significantly increased in Kupffer cells of WT compared with TLR3 mice.

Conclusions: Accumulated hepatic mtdsRNA by alcohol-mediated suppression of PNPase, contributes TLR3 activation of Kupffer cells via exosomal delivery. Consequently, increased IL-1β expression of Kupffer cells triggers IL-17 production of γδ T cells. Therefore, mtdsRNA might be novel therapeutic targets to ALD.



Keywords: Extracellular vesicles, Mitochondrial double-stranded RNA, Mitochondrial degradosome, Alcoholic liver disease

OP-002

Gut-Microbiome Composition and Diversity According to the Progression of Alcoholic Liver Disease

Gi Soo Youn, Min Jea Shin, Haripriya Gupta, Dae Hee Han, Sang Jun Yoon, Na Young Lee, Dong Joon Kim, Ki Tae Suk

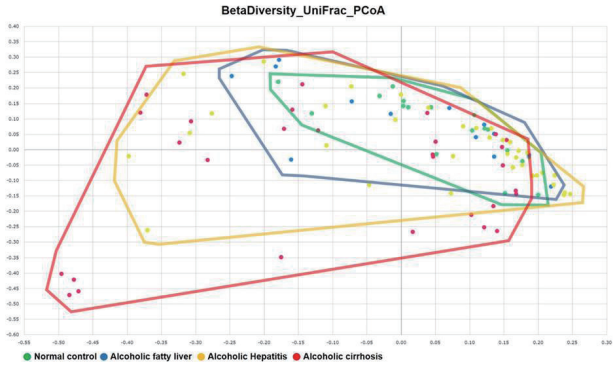
Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea

Aims: Alcoholic liver disease (ALD) is a broad spectrum of disorders including fatty liver, hepatitis, and cirrhosis. Despite intensive research in the last 20 years, there are few internationally approved therapies for treating ALD. We aimed to evaluate specific microbiome composition of ALD and to search therapeutic candidates for ALD treatment through intestinal microbiome analysis.

Methods: Between September 2017 and April 2019, eighteen controls and 72 patients with ALD (age: 55.7±10.9 years, male: 72 [72%]) were prospectively classified as normal control (n=18), fatty liver (n=13), hepatitis (n=35), and cirrhosis (n=29) groups. ALD is defined as liver disease with alcohol consumption history of more than 40 g/day (women) and 60 g/day (men) during the 7 days. Microbiome profiling was conducted with 16S-based Microbial Taxonomic Profiling (MTP) platform of EzBioCloud Apps (ChunLab Inc., Korea). After taxonomic profiling, comparative MTP analyzer of EzBioCloud Apps was used for comparative analysis of groups.

Results: In species richness, alpha diversities (309, 397, 344, and 231) were different and decreased according to the ALD progression (normal control, fatty liver, hepatitis, and cirrhosis, $P<0.05$). Abundant 2 microbiomes in each groups are *Bacteroides plebeius* and *Faecalibacterium prausnitzii* group in normal control, *Prevotella* uc and PAC001304 in fatty liver, *Prevotella* uc and *Bacteroides plebeius* in hepatitis, and *Escherichia coli* group and *B. dorei* in cirrhosis, respectively. In taxonomic biomarker discovery, *F. prausnitzii* group, *Lactobacillus rogosae* group, *Prevotella*_uc, and PAC001304_1 are significantly de-

creasing in abundance according to the ALD progression.



Conclusions: The microbiome compositions are different according to ALD progression. *F. prausnitzii* group, *L. rogosae* group, and *Prevotella*_uc can be developed as therapeutic candidates and future studies are needed for the evaluation of therapeutic target.

Keywords: Alcoholic liver disease, Gut-microbiome

OP-003

Prospective Association of Soybean Products on the Risk of Non Alcoholic Fatty Liver Disease: A Nationwide Population-Based Study

Youn I Choi, Yun Soo Kim, Oh Sang Kwon, Ju Hyun Kim, Seung Kak Shin, and Dong Kyun Park

Division ofHepatology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

Aims: Even though the ingredient of soy product have been ameliorated the prognosis of metabolic inflammation in experiments, there is limited real world data on the prospective effect of soy food consumption on the development of non- alcoholic fatty liver disease (NAFLD).

Methods: We used the data from the Korean Genome and Epidemiology Study_health examinee study (KoGES-HEXA study) obtained during the periods from 2004-2013(baseline) and 2012-2017(follow up study). Soy food intake (soy bean, tofu, soy soup, and soy milk) was assessed through in-person interviews with a validated food-frequency and amount questionnaire. NALFD was defined by fatty liver index (FLI) (>30), or hepatic steatosis index (HSI) (>30). Degree of liver fibrosis (significant fibrosis) was assessed by NAFLD fibrosis score (NFS), FIB-4, and Forns index. To reveal the association of soy food intake at baseline and the risk of newly development of NAFLD and NAFLD associated fibrosis during follow up period, univariate and multivariate analysis were done.

Results: Of 177,231 participants (40–70 year), after exclusion of participants with excess alcohol intake, with baseline FLI or HIS <30, or without follow up data, we finally enrolled 40,224 participants. During median 7.1 year of period, total of 5,160 incidental cases with NAFLD were developed. Soy food consumption was inversely associated with the risk of NAFLD (HR=0.89 [0.88-0.98], *P*=0.04) and NAFLD associated significant fibrosis (HR=0.66 [0.48-0.89], *P*<0.001) in univariate analysis. The Multivariate adjusted HR of the risk of NAFLD and the NAFLD associated significant fibrosis for the upper intake quintile of soy food consumption compared with the lowest quintile were 0.79 (95% CI: 0.70-0.81).

Table 1. Univariate and multivariate analyses producing odds ratio of risk factors for the risk of NAFLD associated significant fibrosis

		NAFLD	Non NAFLD
Soy food consumption	Crude HR[95%CI]	0.66 [0.48-0.89]***	1 (reference)
	Age,sex HR	0.72 [0.51-0.89]**	1 (reference)
	Model 1	0.75 [0.52-0.90]**	1 (reference)
	Model 2	0.76 [0.52-0.92]**	1 (reference)
	Model 3	0.78 [0.55-0.98]**	1 (reference)
	Model 4	0.79 [0.58-0.99]*	1 (reference)

Model1: adjusted for age, sex, and body mass index,
Model2: adjusted for age, sex, body mass index, total Calorie intake,
Model3: adjusted for age, sex, body mass index, total Calorie intake , total protein intake, total lipid intake, smoking, drinking,
Model4: adjusted for age, sex, body mass index, total Calorie intake, total protein intake, total lipid intake, smoking, drinking, exercise, stress index, education, income, and spouse
*P<0.05,**P<0.01,***P<0.001
Abbreviation: NAFLD, non alcoholic fatty liver disease; HR, hazard ratio; 95%CI, 95% confidence interval

Conclusions: In this nationwide population based long-term follow up study, we revealed the soy food consumption had protective effect for the risk of the NAFLD and NAFLD associated with fibrosis.

Keywords: Non alcoholic fatty liver disease, Liver fibrosis, Soy bean, Hazard ratio

OP-004

Evolution of Hepatic Fibrosis and Steatosis during the Long-Term Use of Metformin in Patients with Type 2 Diabetes

Ji Hye Kim[1], Hye Won Lee[1,2], Beom Kyung Kim[1,2], Jun Yong Park[1,2], Do Young Kim[1,2], Sang Hoon Ahn[1,2], Kwang-Hyub Han[1,2], and Seung Up Kim[1,2]

[1]Department of Internal Medicine, Yonsei University, College of Medicine, Seoul, Republic of Korea; [2]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

Aims: The main therapeutic aim in patients with type 2 diabetes (T2D) is to control serum glucose level. Metformin has been widely used as the first-line anti-diabetic drugs. The prevalence of chronic liver diseases such as non-alcoholic fatty liver disease in patients with T2D is high. However, few studies have investigated the evolution of liver fibrosis and steatosis during the long-term use of metformin in patients with T2D.

Methods: Between 2006 and August 2010, patients with newly diagnosed T2D who received metformin were recruited. Patients with chronic liver diseases except non-alcoholic fatty liver diseases, insufficient follow-up period (< 2 years), or insufficient

laboratory information for calculating noninvasive liver fibrosis and steatosis indices (fibrosis-4 index [FIB-4] and hepatic steatosis index [HSI]) at enrollment and at 2 years were excluded. Significant liver fibrosis was defined as FIB-4>2.67 and fatty liver was defined as HSI>36.0.

Results: A total of 1,177 patients were finally enrolled. The mean age of the study population (656 men and 521 women) was 60.7 years. The mean body mass index, serum glucose, hemoglobin A1c, and aspartate and alanine aminotransferase was 25.2 kg/m^2, 141.9 mg/mL, 7.2%, 26.2 IU/L, and 29.5 IU/L, respectively. The mean FIB-4 and HSI was 0.17 and 27.4, respectively. At enrollment, no patient had significant liver fibrosis, but 393 (33.4%) patients had fatty liver. At 2 years of metformin treatment, the mean FIB-4 was significantly increased (0.17 → 1.44), whereas the mean HSI was decreased or maintained (27.4 → 26.6). In addition, significant liver fibrosis was developed in 69 (5.9%) patients, whereas the proportion of patients with fatty liver was decreased or maintained (33.4% → 28.5%). HbA1c level was statistically similar between patients with and without significant liver fibrosis at baseline and 2-years. Only female gender (odds ratio [OR]=3.301, 95% CI, 1.936–5.628, *P*<0.001) was independently associated with the risk of developing significant liver fibrosis at 2-years of metformin treatment. In the subgroup of 702 (59.6%) patients who were follow-up up to 5 years, the FIB-4 tended to increase (mean 1.80 at 5 years), whereas the HSI was maintained (mean 26.6 at 5-years). During the study period (median 97.1 months), 3 (0.3%) and 158 (13.4%) patients developed hepatocellular carcinoma and cardiovascular events, respectively.

Conclusions: During the long-term metformin treatment, female patients with T2D were significantly subject to 3-fold higher risk of liver fibrosis progression. Early recognition of liver fibrosis progression and corresponding medical interventions might be required for female patients with T2D.

Keywords: Diabetes, Metformin, Fibrosis, Steatosis

OP-005

Low Psoas Muscle Mass Is Associated with Advanced Fibrosis in Patients with Biopsy-Proven Non-Alcoholic Fatty Liver Disease

Min Kyu Kang[1], Jung Hun Baek[1], Jung Gil Park[1], Soo Young Park[2], Won Young Tak[2], Young Oh Kweon[2], Se Young Jang[2], Yu Rim Lee[3], Keun Hur[3]

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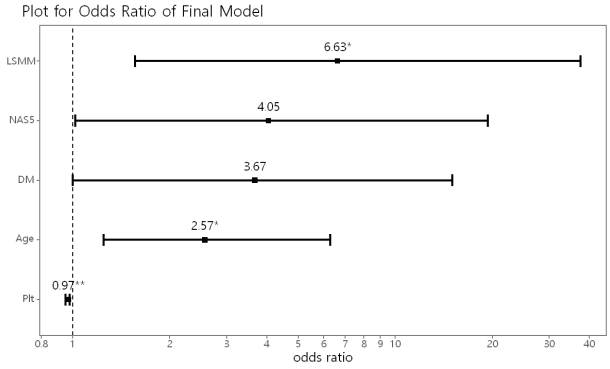
Aims: Association of low skeletal muscle mass (LSMM) and liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) is widely evaluated using indirect and noninvasive modality. Our study is aim to investigate the association between LSMM and advanced liver fibrosis in patient with NAFLD using direct measurement of psoas muscle mass and liver histology.

Methods: We analyzed 146 NAFLD patients who underwent percutaneous liver biopsy and computed tomography, retrospectively. A receiver operating characteristic curve analysis was performed to evaluate optimal cut-off value of psoas muscle index (PMI) for LSMM to predict advanced fibrosis (F3).

Results: The optimal cut-off value of PMI to predict advanced fibrosis was 5.132 cm^2/m^2. On the multivariate analysis, age (odd ratio [OR] 2.57, 95% confidence interval [CI] 1.25–6.30, *P*=0.020), LSMM (OR 6.63, 95% CI 1.56-37.62, *P*=0.017), and platelet counts (OR 0.97, 95% CI 0.95-0.99, *P*=0.000) was associated with advanced fibrosis. The progression of liver fibrosis was negatively correlated with PMI (*r* = -0.364, *P*=0.002).



Conclusions: Low psoas muscle mass is independently associated with advanced fibrosis in patients with biopsy-proven NAFLD.

Keywords: NAFLD, Psoas Muscle, Liver fibrosis

OP-006

Non-Alcoholic Fatty Liver Disease Is an Early Predictor of Metabolic Disease in Metabolically Healthy Population: A Nationwide Claim Data Study

Heejoon Jang[1], Jeong-Hoon Lee[1], Seokhun Yang[2], Soongu Kwak[2], Shinae Kang[3], Seung-Pyo Lee[2], Minseok Albert Kim[1], Sun Woong Kim[1], Cheol-Hyung Lee[1], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Division of Cardiology and Cardiovascular Institute, Seoul, Korea; [3]Division of Endocrinology, Department of Internal Medicine, Yonsei University, Seoul, Korea

Aims: Recent investigations have suggested a bi-directional relationship between non-alcoholic fatty liver disease (NAFLD) and metabolic disease. However, previous studies are limited in providing evidence as to which condition comes first because patients with NAFLD also have several concomitant metabolic syndrome components. The aim of the study is to investigate the impact of NAFLD on the development of metabolic syndrome,

prediabetes/type 2 diabetes, hypertension, and dyslipidemia in a truly metabolically healthy population.

Methods: This analysis included subjects who underwent health evaluation at least twice between 2009 and 2015 from the National Health Insurance Service-National Sample Cohort in Korea (n=28,880). The incidence of metabolic syndrome, prediabetes/type 2 diabetes, hypertension, and dyslipidemia was compared between the NAFLD and the non-NAFLD subjects both in the entire population and in the age, sex, smoking, and body mass index (BMI)-based propensity score-matched population (n=1,092). Univariate and multivariate standard Cox regression model was used to test whether the presence of NAFLD would be an early predictor of the incident metabolic syndrome, prediabetes/type 2 diabetes, hypertension, and dyslipidemia during follow-up.

Results: Presence of NAFLD was associated with significantly higher incidence of future metabolic syndrome, prediabetes/type 2 diabetes, hypertension, and dyslipidemia (age, sex, smoking and BMI-adjusted hazard ratio [aHR]=2.10, 95% confidence interval [CI]=1.18–3.71 for metabolic syndrome [Fig. 1A]; aHR=1.42, 95% CI=1.06–1.90 for prediabetes/type 2 diabetes [Fig. 1B]; aHR=2.36, 95% CI=1.35–4.12 for hypertension [Fig. 1C]; aHR=1.49, 95% CI=1.07–2.06 for dyslipidemia [Fig. 1D]) in the entire cohort.

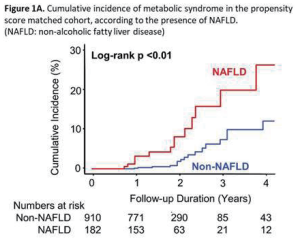


Figure 1A. Cumulative incidence of metabolic syndrome in the propensity score matched cohort, according to the presence of NAFLD. (NAFLD: non-alcoholic fatty liver disease)

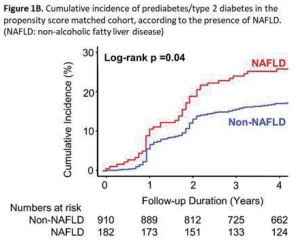


Figure 1B. Cumulative incidence of prediabetes/type 2 diabetes in the propensity score matched cohort, according to the presence of NAFLD. (NAFLD: non-alcoholic fatty liver disease)

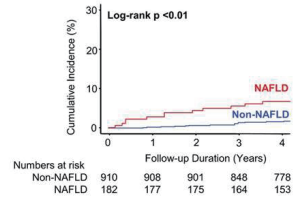


Figure 1C. Cumulative incidence of hypertension in the propensity score matched cohort, according to the presence of NAFLD. (NAFLD: non-alcoholic fatty liver disease)

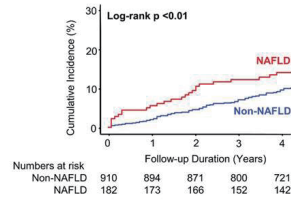


Figure 1D. Cumulative incidence of dyslipidemia in the propensity score matched cohort, according to the presence of NAFLD. (NAFLD: non-alcoholic fatty liver disease)

Conclusions: The current study showed significant associations of NAFLD with the incidence of metabolic diseases in a non-obese population with none of the metabolic syndrome components. This enabled us to focus on the predictive impact of NAFLD on future incident metabolic syndrome, in isolation from other known metabolic confounders.

Keywords: Non-alcoholic fatty liver disease, NAFLD, Predictor, Metabolic disease

OP-007

Valine and Leucine Suppresses Hepatic Stellate Cells Activation via TGF-β Signaling Inhibition

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Aims: Epithelial-mesenchymal transition (EMT) plays a role in the development fibrosis for the hepatic stellate cells (HSCs). Recent studies suggested that branched-chain amino acid (BCAA; valine, leucine, and isoleucine) can suppress the incidence of hepatocellular carcinoma and ameliorate hepatic fibrosis progression but it is not clear what component is working effectively. This study aimed to evaluate the anti-fibrotic effect of valine and leucine in LX-2 cells (human HSCs).

Methods: To check the cell viability by BCAA, conducted a test on LX-2 cells and determined the concentration to be treated in LX-2 cells. LX-2 cells were starved in 1/2 medium (Zero media + DMEM HG) for 24 h prior to treatment with TGF-β1. LX-2 cells were activated with TGF-β1 (2.5 ng/㎖), and then were treated with different concentration of valine and leucine (0, 5, 10 and 20 mM for 24 or 48 hours). Evaluation of the anti-fibrotic effect of BCAA on LX-2 cells was evaluated by the quantitative real-time polymerase chain reaction (qRT-PCR) and western blotting.

Results: The mRNA expressions of fibrotic gene (COL1α1) and EMT transcription factors (SNAI1, and SNAI2) were increased in TGF-β1 treated LX-2 cell. And the protein expression of fibrosis marker (α-SMA) was increased in TGF-β1 treated LX-2 cell. But the mRNA expressions and protein expression were decreased in valine or leucine treated LX-2 cell that was stimulated by TGF-β1. Furthermore, protein expression of p-P38 and p-SMAD 2/3 were decreased in valine or leucine treated activated cell. Activation of LX-2 cells by TGF-β1d was inhibited in proportion to the concentration of valine and leucine.

Conclusions: Leucine and valine inhibit TGF-β1 induced SMAD and P38 signaling to repress the progression to liver fibrosis. And this research suggests BCAA supplementation would be beneficial for patient with liver fibrosis

Keywords: Valine, Leucine, Hepatic fibrosis, EMT, TGF-β1 signaling

OP-008

Molecular Diagnosis of Glycogen Storage Disease Type IX Using GSD Gene Panel

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Aims: Glycogen storage disease type IX (GSD IX) is caused by a deficiency of hepatic phosphorylase kinase (PhK). GSD type IX has been reported to be uncommon in Korea. The aim of this study is to clarify the clinical features and mutation analysis of GSD IX in Korea.

Methods: GSD gene panel was performed in GSD patients whose types were unknown at Seoul National University Hospital. GSD gene panel using hybridization capture-based next-generation sequencing contained *AGL, G6PC, GBE1, GYS2, PHKA2, PHKB, PHKG2, PYGL, SLC2A2*, and *SLC37A4*. The median duration of follow up period was 8.3 years.

Results: Nine children presented with hepatomegaly and serum ALT elevation. Among them, hypoglycemia was found in 2 (22%), hyperuricemia in 5 (56%), hypertriglycedemia in 9 (100%), hyperlactacidemia in 5 (56%), short stature in 4 (44%), and hepatic fibrosis on liver biopsy in 7 (78%). Seven *PHKA2* mutations were identified in 8 patients with GSD IXa; 1 nonsense (p.Asp757Ter), 2 splicing (c.918+1G>A, c.718-2A>G), 1 frameshift (p.Asp136ProfsTer11) and 3 missense mutations (p.Gly1210Arg, p.Glu415Asp, and p.Arg916Trp). Two mutations of *PHKG2* were identified in children with GSD IXc; 1 frameshift (p.Ser262AlafsTer6) and 1 missense (p.Val221Met). Eight novel mutations are identified in Korean children with GSD IX.

Conclusions: GSD gene panel is a very useful diagnostic tool to confirm GSD type IX. GSD type IX is not rare in Korea. Liver enzymes and hypertriglyceridemia in children with GSD IX tended to improve with age.

Keywords: Glycogen storage disease, Molecular diagnosis, Gene panel

OP-009

A Coagulation Factor IX-Deficient Rat as a Translational Pre-Clinical Model of Severe Hemophilia B

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Aims: Hemophilia B (HB) is characterized by coagulation factor IX (FIX) deficiency due to genetic mutation of *F9*. Patients with severe HB, which accounts for 60% of all HB cases, exhibit <1% of FIX in the blood and have frequent spontaneous bleeding episodes which can affect life-span of affected patients. *F9-/-* mouse was generated in an attempt to recapitulate features of human hemophilia B. However, these mice failed to exhibit spontaneous bleeding phenotype. Therefore, an animal model that can reflect phenotypes of severe HB is required. Rats can be a great candidate for pre-clinical animal model for human hemophilia B as more circulating blood allows robust analysis from peripheral blood serum. Therefore, we generated and novel *F9-/-* rat using CRISPR/Cas9 system.

Methods: *F9-/-* rats were generated by CRISPR/Cas9-based electroporation system. Briefly, we electroporated rat embryos with Cas9 and gRNAs targeting exon 2 of rat *F9*. F2 generation of *F9-/-* rats were utilized for genotyping and phenotypic analyses. Phenotypic analyses include measurement of FIX activity, serum analysis of prolonged activated partial thromboplastin time (APTT), clot formation time and assessment of spontaneous bleeding using constant monitoring and histology.

Results: Majority of homozygous *F9-/-* rats exhibited spontaneous hemorrhagic episodes with severe. The *F9-/-* rats had no detectable FIX activity and showed a significantly prolonged activated partial thromboplastin time (APTT) along with clot formation time when compared with wild-type littermates which phenocopies severe human hemophilia B patients.

Conclusions: Unlike *F9* mutant mice, our novel *F9-/-* rats fully mimic severe human HB phenotypes by not only prolongs clot formation time upon injury but also displayed spontaneous internal bleeding primarily associated with musculoskeletal diasese. In conclusion, novel *F9-/-* rat strain can be a valuable pre-clinical model for severe HB.

Keywords: Hemophilia B, CRISPR/Cas9, Rat, Coagulation factor IX

OP-010

MicroRNA-101-3p Suppresses Hepatic Stellate Cell Activation and Promotes the Hepatic Differentiation of Human Bone Marrow-Derived Mesenchymal Stem Cells

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Aims: Although the therapeutic mechanisms of bone marrow-derived mesenchymal stem cells (BM-MSC) are still unclear, BM-MSCs play key therapeutic roles in liver fibrosis. Furthermore, microRNAs (miRNAs) are regulators in hepatic differentiation and liver fibrosis. miR-101-3p is upregulated during hepatic trans-differentiation, whereas miR-101-3p is downregulated in a stage of liver fibrosis. The purpose of this study is to

investigate miR-101-3p's roles in the hepatic differentiation of human BM-MSC (hBM-MSCs) and in hepatic stellate cell (HSC) activation.

Methods: To detect the miRNAs of hBM-MSC into functional hepatocytes and liver fibrotic tissue, the next-generation sequencing (NGS) was performed in hBM-MSCs before and after differentiation, hepatocyte, normal liver tissue, portal fibrotic tissue, and septal fibrotic tissue. To determine the effects miR-101-3p, hBM-MSC was treated with mimic or inhibitor during the hepatic differentiation. HSC LX2 was treated with TGF-β1 (2.5 ng/㎖), and with or without miR-101-3p mimics. The role of miR-101-3p was identified through the change of liver-specific genes, EMT markers, and fibrosis genes using the quantitative real-time PCR (qRT-PCR) and western blotting.

Results: As a result of NGS analysis, miR-101-3p showed a higher expression level in differentiated hepatocyte-like cells and hepatocyte than hBM-MSC but lower expression level in liver fibrosis than normal liver. miR-101-3p caused the increase in the liver-specific gene (ALB and HNF4α) in hBM-MSC, while mesenchymal markers (SNAI1 and CDH2) and fibrosis markers (α-SMA and COL1α1) decreased in hBM-MSC and LX2. As a result, miR-101-3p mimic promoted the hepatic differentiation of hBM-MSC and inhibited the TGF-β1 mediated LX2 activation.

Conclusions: In this study, we identified miR-101-3p that can regulate the hepatic differentiation of hBM-MSC and the hepatic fibrosis. Our results demonstrate that miR-101-3p may be a biomarker, monitoring the response to therapeutic effect by BM-MSC in liver fibrosis.

Keywords: Human bone marrow-derived mesenchymal stem cells (hBM-MSCs), Hepatic differentiation, Next-generation sequencing (NGS), microRNAs (miRNAs), Fibrosis

OP-011

Effect of Sericin Peptide in Animal Models of Non-Alcoholic Steatohepatitis (NASH)

Hyeon Tae Kang, Na Ryung Choi, Dae Won Jun, Jin Hwa Park, Dae Hyun Lim, Won Wu Seo, Ji Hyun Yeo, Jai Hoon Yoon, Kang Nyeong Lee, Hang Lak Lee, Oh Young Lee, Byung Chul Yoon, and Ho Soon Choi

Department of Inernal Medicine, Hanyang University College of Medicine, Korea

Aims: Sericin, a silk protein, is a component of cocoon. Previous studies have shown that sericin improves mitochondrial function in an animal model of metabolic disease. However, it is not yet known whether sericin is effective in non-alcoholic fatty liver disease.

Methods: 6 weeks old C57BL/6 mouse used. Forty mice were divided into four groups. Sericin and saline administrated for 17 weeks in chow and 60% high fat diet groups, respectively. Liver biopsy, blood test, oral glucose tolerance test were performed in all animal groups. Electro-microscopy was performed to check mitochondrial function in liver tissue.

Results: There was no difference in body weight and diet intake during the study period between the control and sericin groups. However, liver weight and liver / body weight ratio were significantly lower in sericin group than in control group. In the sericin group, the AUROC of the oral glucose tolerance test was lower than that of the control group. Hepatic *p*JNK/JNK ratio, and *p*Akt/Akt ratio was decreased in active treatment group. Degree of hepatic steatosis and inflammation were lesser compared to the control group in the sericin treated group. NAS scores were also lower in treatment group. Serum ALT, AST and triglyceride levels were significantly lower in sericin treated group than in control group. TNF-α and IL-6 expression was lower in liver tissues in the sericin group compare to control group. Electron microscopic findings showed abnormal mitochondria restored in sericin treated group.

Conclusions: Sericin reduced intrahepatic fat amount and intrahepatic inflammation in non-alcoholic fatty liver disease animal models.

Keywords: Sericin, Animal model, NASH

OP-012

Amoxicillin Induced Histopathological Changes in the Liver and Other Organs of Albino Rats

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Aims: Amoxicillin is a widely prescribed antibiotic and has adverse effects like dirrhoea, hepatotoxicity and hypersensitivity. This study aims to evaluate the histopathological changes in the liver and other organs of albino rats after the administration of amoxicillin.

Methods: This study was conducted at the pharmacy, pharmacology and pathology department of Gandaki Medical College in the period of four months from January till April, 2018. Albino rats (n=12, six test, six control) of 200 to 220g were kept under optimum laboratory conditions and amoxicillin was administered for 10 days. The rats were sacrificed under diazepam and ketamine anesthesia after 10 days and samples of liver, brain, heart, kidney and testis were collected in phosphate buffer. The samples were then sent for histopathological investigation after fixing with 10% formalin solution and cutting into 4 to 5 µm thick sections. The slides were prepared with hematoxylin and eosin stain and microscopic studies done under high power field.

Results: The test rats suffered from chronic diarrhea from the intake of medication till sacrifice. The liver function test showed elevation of liver enzymes in the test rats. The histopathological investigation of liver of test rats showed congestion of central vein, hemorrhage and hydropic changes in hepatocytes. The brain showed shrunken neurons surrounded by perineuronal vacuolations. In the heart, there was disruption of cardiac muscle fibers with pyknotic nuclei of cardiomyocytes. The testes

were shrunken, and some seminiferous tubules were atrophied. There were severe degenerative changes in glomerulus and tubules of kidney in the form of hyper cellularity with reduced urinary space.

Conclusions: Amoxicillin has shown toxicity to the liver, brain, kidneys, heart and testes in albino rats. Therefore, it needs special precautions when prescribing to humans.

Keywords: Amoxicillin, Drug induced liver damage, Hepatotoxicity, Toxicity

[Group 3] June 21, 2019 | 15:30-16:30

HBV

OP-013

Comparative *Ex Vivo* Analyses of Hepatitis B Virus-Specific CD8+ T Response between Patients Considered Immune Tolerant and Patients on Antiviral Treatment

Pil Soo Sung[1,2,#], Dong Jun Park[2,#], Jung-Hee Kim[2], Ji Won Han[3], Eun Byul Lee[2], Gil Won Lee[2], Hee Chul Nam[2,4], Jeong Won Jang[2,4], Si Hyun Bae[1,2], Jong Young Choi[2,4], Eui-Cheol Shin[3], Su-Hyung Park[3], Seung Kew Yoon[2,4*]

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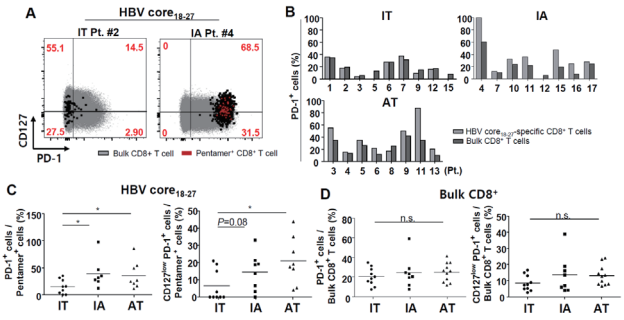
Aims: Although it is generally accepted that perinatal transmission of hepatitis B virus (HBV) leads to chronic persistent infection, the underlying mechanism has not been clearly elucidated. Until recently, HBV-infected children in the IT phase were considered to have defects in mounting effective humoral and T cell responses against the infecting virus. In this study, we aimed to detect and characterize the *ex vivo* virus-specific $CD8^+$ T cells in patients considered immune-tolerant and under antiviral treatment.

Methods: We investigated a Korean chronic hepatitis B cohort comprising 15 patients in the immune-tolerant phase, 17 in the immune-active phase, and 13 under antiviral treatment. We performed enzyme-linked immunospot (ELISpot) assays *ex vivo* and intracellular cytokine staining after *in vitro* culture using a mixture of human leukocyte antigen A2-restricted epitopes and overlapping peptides of HBV proteins. We also performed *ex vivo* multimer staining assays and examined the expression of exhaustion markers and transcription factors in pentamer-positive cells.

Results: *Ex vivo* ELISpot revealed that HBV-specific T cell function was weaker in immune-tolerant patients than in those under antiviral treatment. Short-term culture of peripheral blood mononuclear cells revealed that some immune-tolerant patients had HBV-specific $CD8^+$ T cells able to produce interferon-γ. We detected HBV-specific $CD8^+$ T cells *ex vivo* (using the HBV $core_{18-27}$ and HBV $polymerase_{455-463}$ pentamer) in patients from all three groups. Pentamer-stained HBV-specific $CD8^+$ T cells were defective in IFN-γ secretion in patients in the IT group, although those of some patients in AT group showed *ex vivo* IFN-γ secretion after peptide stimulation. The PD-1^+ subset of pentamer$^+$ $CD8^+$ T cells was smaller *ex vivo* in the immune-tolerant phase than in the immune-active phase or under antiviral treatment. Moreover, we found that the proportion of CD-127^{low}PD-1^+ HBV-specific $CD8^+$ T cells was significantly lower in patients in the IT phase than in those in the AT phase. Interestingly, the proportion of PD-1^+ $CD8^+$ T cells and $CD127^{low}$PD-1^+ HBV-specific $CD8^+$ T cells in HBV-specific $CD8^+$ T cells correlated with patient age.



Conclusions: Overall, HBV-specific $CD8^+$ T cells are present in patients considered immune-tolerant, although their *ex vivo* functionality is weaker than in patients under AT. Despite the high viral load, the proportion of PD-1 expression in HBV-specific $CD8^+$ T cells is lower in the immune-tolerant phase than in AT phases.

Keywords: Hepatitis B virus, CD8 T cell, Immune tolerant

OP-014

Extremely Low Risk of Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients with Immune Tolerant Phase: A Multicenter Retrospective Cohort Study

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Aims: Patients in immune tolerant phase (IT-phase) of chronic hepatitis B (CHB) is not indicative of antiviral therapy (AVT). We investigated the cumulative incidence of HCC in patients in IT-phase, independent predictors of phase change and HCC development, and proposed the optimal cutoff HBV DNA level to define IT-phase.

Methods: A total of 946 consecutive patients in IT-phase between 1989 and 2017 were enrolled from 8 Korean tertiary hospitals. IT-phase was defined as hepatitis B e antigen positive, HBV-DNA >20,000 IU/ml, and alanine aminotransferase (ALT, ≤40 IU/L). ALT cutoff by KASL guideline was defined as 34 for men and 30 for women.

Results: The mean age of the study population (429 men and 517 women) was 36.7 years. The mean ALT and HBV DNA level was 24.6 IU/L and 316,310,000 IU/mL, respectively. No patient had liver cirrhosis. Of the study population, 476 (50.3%) stayed persistently in IT-phase, whereas 23 (2.4%), 116 (12.4%), and 331 (35.0%) patients experienced phase change into inactive carrier, minimally active, and immune active phase requiring AVT during the study period (median 63.6 [interquartile range {IQR} 29.3-103.2] months). The cumulative incidence of HCC at 10-years was 0.1%. When patients were censored at the time of phase change, the cumulative incidence was 0.2% (median follow-up 35.7 [IQR 18.0-70.4] months). On multivariate analysis, older age was the only predictor of HCC development (hazard ratio [HR]=1.067, 95% confidence interval [CI], 1.003-1.134) (*P*=0.038). On multivariate analysis, higher HBV DNA level > 10^7 IU/mL was independently associated with the reduced risk (HR=0.675, 95% CI, 0.540-0.844, *P*=0.001), whereas high ALT level above the cutoff by KASL guideline (HR=2.121, 95% CI, 1.717-2.620, *P*<0.001) was independently associated with higher risk of phase change from IT-phase to others.

Conclusions: Patients in IT-phase of CHB had an extremely low risk of HCC development. Thus, AVT should be cautiously considered for this population. In addition, we found that older age was the predictor of HCC development and that HBV DNA level > 10^7 IU/mL which independently predicted phase change from IT-phase might be used to define IT-phase.

Keywords: Immune tolerant, Hepatitis B, Hepatocellular carcinoma, HBV DNA

OP-015

Three Year Efficacy and Safety of Tenofovir Alafenamide (TAF) Compared to Tenofovir Disoproxil Fumarate (TDF) in Chronic Hepatitis B (CHB) Patients

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Aims: In 2 identically-designed double-blind, randomized (2:1), Phase 3 studies, the safety and efficacy of TAF vs TDF was evaluated in subjects treated for 3 years.

Methods: 1298 HBeAg-negative and HBeAg-positive CHB patients were randomized and treated with TAF 25 mg or TDF 300 mg QD. Included in this analysis, were 1118 patients (759 HBeAg-positive and 359 HBeAg-negative); 866 of whom received TAF and 252 who received TDF for 3 years. Efficacy analyses included virologic, biochemical, and serologic responses, and pooled safety assessments included changes in bone mineral density (BMD), serum creatinine, and estimated GFR by Cockcroft- Gault method (eGFRCG).

Results: Baseline characteristics were similar between groups; mean age 39 years, 63% males, 78% Asian mostly genotypes C (48%) and D (26%); mean HBV DNA was 7.0 log10 IU/mL (34% had HBV DNA ≥ 8 log10 IU/mL), and 25% previously treated with nucleos(t)ides. At Week 144, high rates of virologic control were maintained in TAF vs. TDF subjects; a greater proportion of TAF vs TDF patients achieved ALT normalization (Table). Overall, adverse events (AEs) and serious AEs were similar between groups. At Week 144, greater median declines in eGFRCG were observed with TDF treatment; similarly, hip and

spine BMD declines in the TDF group were larger than in the TAF group (Table).

Table: Efficacy and Safety (Renal and Bone) Results at Year 3

	HBeAg Negative (Study 108)		HBeAg Positive (Study 110)	
Efficacy Parameters[a]	**TAF (N=285)**	**TDF (N=74)**	**TAF (N=581)**	**TDF (N=178)**
HBV DNA <29 IU/mL, n/N (%)	247 (87)	62 (84)	423 (80)	123 (82)
P value	0.56		0.46	
HBV DNA, mean (SD) change (log_{10} IU/mL)	-4.27 (1.41)	-4.27 (1.28)	-5.94 (1.44)	-6.07 (1.39)
ALT normalization (AASLD 2018 criteria), n/N (%)[b]	188/264 (71)	43/73 (59)	359/517 (69)	88/144 (61)
P Value	0.05		0.06	
HBeAg loss n/N (%)	N/A	N/A	133/565 (26)	36/175 (25)
HBsAg loss n/N (%)	1/281 (0.4)	0/74	8/576 (1.5)	3/177 (2)
Pooled Renal and Bone Parameters[c]	**TAF**		**TDF**	
$eGFR_{CG}$, median (Q1, Q3) change (mL/min)	n= 748 -1.2 (-9.6, +7.2)		n= 198 -6.0 (-15, +2.4)	
P value	<0.001			
Hip BMD, mean (SD) % change	n=713 -0.40 (2.97)		n=187 -2.505 (3.66)	
P value	<0.001			
Spine BMD, mean (SD) % change	n=720 -0.498 (3.83)		n=191 -2.09 (4.46)	
P value	<0.001			

[a]Efficacy results are missing = failure unless otherwise specified; [b]ULN ≤35 U/L (males), ≤25 U/L (females); [c]Safety results are missing=excluded
$eGFR_{CG}$ is creatinine clearance by Cockcroft-Gault method, BMD is bone mineral density by dual energy x-ray absorptiometry (DXA), Q is quartile

Conclusions: After three years of treatment, high and similar rates of virologic suppression were achieved and maintained and continued improvements in renal and bone safety were observed in patients receiving TAF compared to TDF.

Keywords: TAF, TDF, 144 weeks, CHB

OP-016

Predictive Score for Hepatocellular Carcinoma after Hepatitis B E Antigen Loss in Patients Treated with Entecavir or Tenofovir Disoproxil Fumarate

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Aims: The risk of developing hepatocellular carcinoma (HCC) after hepatitis B e antigen seroclearance (ESC) remains unclear. We established and validated a new risk prediction model for HCC development after ESC in patients with chronic hepatitis B (CHB) receiving antiviral therapy (AVT).

Methods: Between 2006 and 2016, 769 patients (training cohort) and 1,061 patients (validation cohort) with CHB who experienced ESC during AVT using entecavir (ETV) or tenofovir disoproxil fumarate (TDF) were recruited.

Results: In the multivariate analysis, male sex (hazard ratio [HR]=2.092; 95% confidence interval [CI]=1.152–3.800), cirrhosis (HR=5.141; 95% CI=2.367–11.167), and fibrosis-4 index (FIB-4) of >3.25 (HR=2.070; 95% CI=1.184–3.620) were the independent risk factors for HCC development (all P<0.05). Accordingly, a novel HCC-ESC_{AVT} model was developed (1x[sex: male=1, female=0]+3x[cirrhosis=1, non-cirrhosis=0]+1x[FIB-4: >3.25=1, ≤3.25=0]). The cumulative risk for HCC development was significantly different among the risk groups based on the HCC-ESC_{AVT} category (0–1, 2–4, and 5 for the low-, intermediate-, and high-risk groups, respectively) (overall P<0.001, log-rank test). The area under the receiver operating characteristic curve (AUC) for predicting HCC development 3, 5, and 10 years after ESC was 0.791, 0.791, and 0.790, respectively (all P<0.05). The predictive value of the HCC-ESC_{AVT} model was similar in the validation cohort (AUC=0.802, 0.774, and 0.776 at 3, 5, and 10 years, respectively; all P<0.05).

Conclusions: A new HCC-ESC_{AVT} model, which includes male sex, cirrhosis, and FIB-4 of >3.25 as constituent variables, for HCC development after ESC during AVT was established and well validated in this study.

Keywords: Hepatocellular carcinoma, Hepatitis B, Hepatitis B e antigen, Risk prediction

OP-017

Establishment of HBV-Replicating Mice Model from a Korean HBV Genome with Defective HBV-Specific T Cell Responses

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Aims: Lack of a small animal model mimicking the human chronic hepatitis B virus (HBV) infection hampers developing the new immune-stimulating methods. We aimed to establish a mouse model that harbors replicating genotype C HBV derived from a Korean patient and to investigate HBV-specific T cell responses in the established mouse model.

Methods: pAAV_HBV 1.3 plasmid containing a greater-than-genome-length HBV genotype C fragment derived from a Korean patient (nt 1073–3215–2067. GeneBank: DQ683578.1) was constructed. To induce HBV replication in mouse liver, pAAV_HBV1.3 or pAAV-MCS was injected into the tail veins of mice. Serum levels of HBsAg were determined using the Enzyme-Linked immunosorbent assay kit. For the Enzyme-linked immunospot (ELISPOT) assay with mouse T cells, splenocytes were stimulated with overlapping peptides (OLPs).

Results: After HDI of the constructed plasmid, we monitored serum HBsAg levels in young (6-week-old) CBA/caj mice. By 20 days post-HDI, serum HBsAg was detected and the level declined but remained detectable until 60 days. All mice sera were HBsAg positive at 50 days after injection, but the ALT level was not increased in mice. At 8 weeks post HDI, immunohistochemical staining for HBsAg in liver cells from infected mice revealed numerous hepatocytes expressing the HBV protein. The ELISpot assay with splenocytes demonstrated that HBV-transfected CBA/caj mice had a very low level of IFN-γ-producing HBV-specific T-cells *ex vivo* after being stimulated with HBcAg and HBsAg OLPs. Following intracellular cytokine staining also demonstrated poor production of IFN-γ by HBV-specific $CD8^+$ T cells *ex vivo* after being stimulated with HBcAg and HBsAg OLPs.

Conclusions: We established a nontransgenic hydrodynamic transfection mouse model with HBV genotype C replication derived a Korean patient. with very low levels of interferon-γ-producing HBV-specific T-cells. This model mimics the immune tolerant phase of chronic HBV infection, and can be applied to the development of immunostimulatory therapeutics against HBV.

This research was supported by BrainKorea21.

Keywords: Hepatitis B virus, Mouse model, T cell

OP-018

Entecavir versus Lamivudine as Antiviral Prophylaxis for Patients with Hepatitis B Infection Undergoing Anticancer Cytotoxic Chemotherapy: A Randomized, Multicenter Clinical Trial

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Aims: Entecavir (ETV) is preferred to lamivudine (LAM) for the treatment of chronic hepatitis B (CH-B); however, it is unclear whether ETV would be more effective than LAM in the prophylactic setting for patients with anticancer chemotherapy. The aim of this study was to compare the efficacy and safety of ETV vs. LAM in preventing hepatitis B virus (HBV) reactivation in CH-B patients with solid and hematologic malignancies undergoing cytotoxic chemotherapy.

Methods: Randomized, open-label, controlled phase 3 study was conducted from April 2012 to June 2017 at 5 tertiary hospitals in South Korea. The study subjects were antiviral-naïve 180 CH-B patients who were indicated to antiviral therapy, but not reimbursed by the National Health Insurance in 2012, and had a plan of curative or (neo)adjuvant chemotherapy for their solid (91%) or hematologic (9%) malignancies. They were allocated into either the LAM (n=92) or ETV (n=88) treatment group, stratified by malignancy types (solid or hematologic) and study sites, and received study medication until 24 week after completion of the last chemotherapy. The primary outcome was HBV reactivation, defined as either virologic breakthrough during antiviral therapy or withdrawal flare of HBV DNA level during 24 weeks after discontinuation of antivirals. Secondary outcomes included HBV-related hepatitis, emergence of genotypic resistance, hepatic decompensation, and chemotherapy disruption (TRIAL REGISTRATIONS clinicaltrials.gov Identifier: NCT01580202).

Results: On ITT analysis, HBV reactivation developed in 54.4% and 47.1% in the LAM and ETV groups, respectively (Odds ratio, 1.3; 95% confidence interval, 0.7-2.4; *P*=0.330). In the ETV group, the virologic breakthrough rate was significantly lower than in the LAM group, and HBV resistance was only observed in the LAM group. While development of hepatitis flare was not different between the 2 groups, chemotherapy disruption was more frequently encountered in the ETV group.

	Lamivudine (n=90)	Entecavir (n=87)	Difference (95% CI), %	Odds Ratio (95% CI)	P-value
HBV reactivation	49 (54.4%)	41 (47.1%)	7.3 (-7.4, 22.0)	1.3 (0.7, 2.4)	0.330
Virologic breakthrough	12 (13.3%)	1 (1.1%)	12.2 (4.8, 19.6)	13.5 (1.7, 108.1)	0.008
Withdrawal flare	37 (41.1%)	40 (46.0%)	-4.9 (-19.5, 9.7)	1.0 (0.6, 1.9)	
HBV-related hepatitis flare	4 (4.4%)	1 (1.1%)	3.3 (-1.5, 8.1)	4.0 (0.4, 36.5)	0.368
HBV resistance	3 (3.3%)	0 (0.0%)	3.3 (-0.4, 7.0)	3.0 (0.5, 30.4)	0.246
Chemotherapy disruption	1 (1.1%)	8 (9.2%)	-8.1 (-14.5, -1.6)	0.1 (0.0, 0.9)	0.017

Conclusions: Among CH-B patients with predominantly solid cancers on cytotoxic chemotherapy, ETV did not result in significant reduction of HBV reactivation compared with LAM. However, ETV significantly reduced the incidence of virologic breakthrough during antiviral prophylaxis compared with LAM. When prolonged chemotherapy would be expected, ETV may be preferred to LAM as an optimized prophylactic antiviral agent.

Keywords: Hepatitis B virus, Chemotherapy, Lamivudine, Entecavir

[Group 4] June 21, 2019 | 15:30-16:30

Cirrhosis & Liver Failure

OP-019

Low Apoprotein A1 as an Indicator of Poor Prognosis in Patients with Liver Cirrhosis

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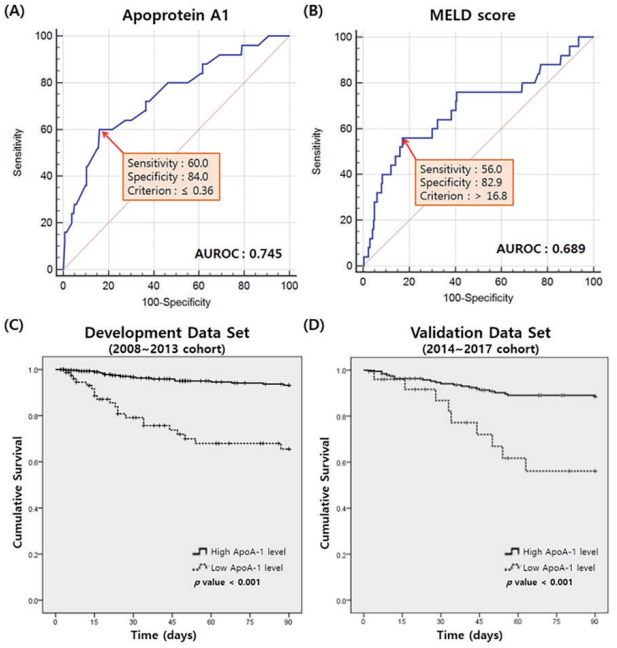
Aims: Liver cirrhosis has an appalling prognosis and numerous methods for predicting the prognosis have been extensively developed. The aim of this study was to investigate the value of apoprotein A1 in cirrhotic patients.

Methods: We retrospectively reviewed data from liver cirrhosis patients who were admitted from 2008 to 2017 in Chonbuk University Hospital. The development cohort included the first six-year populations, and the validation cohort included the following four-year populations. Apoprotein A1 level of individuals during admission was also required. Demographics and clinical parameters were evaluated and analyzed.

Results: 387 patients (296 men and 91 women) with liver cirrhosis were included for the development data set. There were 38 non-survivors (9.8%) during the 90-day follow-up, and apoprotein A1 level was significantly lower in this group (0.5 ± 0.4 vs 0.8 ± 0.4, *P*<0.001). The receiver operating characteristic (ROC) curve was used to evaluate the prognostic performance of apoprotein A1, and the area under ROC curve was 0.745 and the calculated optimal cut-off value was 0.36 g/L (sensitivity 60.0, specificity 84.0). We divided the patients into two groups regarding the apoprotein A1 level. Lower age, higher WBC counts, higher PT levels, lower sodium levels, higher AST and ALT levels, higher CRP levels, lower cholesterol and HDL cholesterol levels, higher CTP scores and higher MELD scores were revealed in the low apoprotein A1 group (≤ 0.36g/L) with statistical significance. The 90-day survival rate was analyzed using Kaplan-Meier curve with log-rank test and survival rate was significantly lower in the low apoprotein A1 group (*P*<0.001). The validation data set included 217 patients and there were 30 non-survivors (13.8%) during the 90-day follow-up. The 90-day survival rate in the validation data set was also significantly lower in the low apoprotein A1 group (*P*<0.001).



Conclusions: Low apoprotein A1 level considerably indicated severe disease status and was strongly associated with poor survival rate in patients with liver cirrhosis. Apoprotein A1 can be a useful marker to predict the prognosis of liver cirrhosis.

Keywords: Liver cirrhosis, Apolipoprotein A-I, Prognosis, Survival rate

OP-020

Adipose Tissue Distribution in Relation to Insulin Resistance in Patients with Cirrhosis

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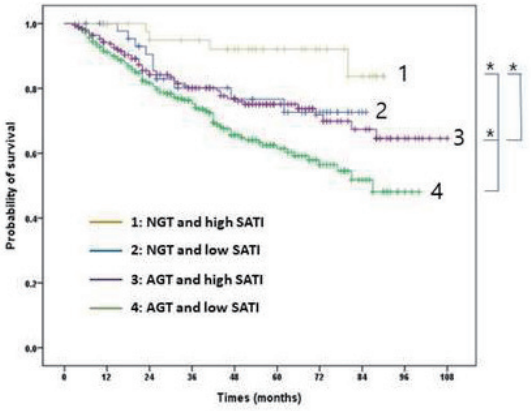
Background: Although muscle mass and adipose tissue are associated with the risk of diabetes in the general population, it remains controversial in cirrhosis. We evaluated the association and impact on the survival adipose distribution (subcutaneous adipose tissue index [SATI] and visceral adipose tissue index [VATI]), sarcopenia, and abnormal glucose tolerance in cirrhosis.

Methods: This prospective observational study included 550 cirrhotic patients who underwent a 75-g oral glucose tolerance test and computed tomography. The patients were divided into normal glucose tolerance (NGT) and abnormal glucose tolerance (AGT) groups of patients with either impaired glucose

tolerance (IGT) or diabetes mellitus (DM). The cut-off values for high SATI or VATI were adopted if they were higher than the mean for females (SATI, 68.01; VATI, 35.95) and males (SATI, 35.98; VATI, 37.76).

Results: Among the patients, NGT was diagnosed in 93 (16.9%), AGT in 457 (83.1%), IGT in 33.8% and DM in 49.3%. The proportions of sarcopenia (50.0 vs. 50.0%), high SATI (52.3 vs. 47.7%) and high VATI (51.8 vs. 48.2%) were not significantly different between the NGT and AGT groups. During a median follow-up period of 42.0 months, the survival in the high SATI group was higher than low SATI in the AGT group (log-rank *P*=0.014), whereas survival was not different in the NGT group (*P*=0.070). In a subgroup analysis, survival of a high SATI was higher than that of low SATI in CTP class A (*P*=0.035), whereas survival was not different in CTP class B/C (*P*=0.523). Sarcopenia and high VAT was not associated with mortality in either NGT or AGT.



Conclusions: A high SATI was beneficial for survival in patients with abnormal glucose tolerance, particularly in those with compensated cirrhosis. However, sarcopenia and VATI were not associated with mortality in abnormal glucose tolerance.

Keywords: Cirrhosis, Adipose tissue, diabetes mellitus, Impaired glucose tolerance

OP-021

Efficacy of Thromboelastography for Predicting Prognosis of Korean Patients with Cirrhosis

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Aims: Thrombocytopenia and prothrombin prolongation are common clinical features in patients with liver cirrhosis. However, deficiency of fibrinolysis factors was also accompanied. Therefore, identification of cirrhotic patient's hemostatic status by conventional parameters alone can mislead to wrong treatment. This study tried to evaluate the association between results of thromboelastography (TEG), which directly reflect hemostasis, and the prognosis of patients with cirrhosis.

Methods: We prospectively enrolled patients with cirrhosis and performed TEG. Patients with malignancy under treatment, and those with chronic kidney disease were excluded. Primary outcome was defined as development of major bleeding events within one month from enrollment, which are severe bleeding requiring hospitalization or transfusion. Secondary outcomes were death or urgent liver transplantation, occurrences of variceal bleeding, overt encephalopathy and portal vein thrombosis within one month.

Results: A total of 85 patients were enrolled, with an average age of 60.2 ± 10.7 years and male predominance (65.9%). Alcohol accounted for 62.4% of etiologies of cirrhosis and 54.1% of patients had Child-Pugh class A. The maximum amplitudes and angles from TEG were correlated with the platelet count (*r*, 0.764 and 0.652; all *P*<0.001). During one month after enrollment, major bleeding events were developed in 16 patients, and were significantly associated with K time, maximum amplitude, angle and lysis30 from TEG, platelet count, INR in logistic regression analyses. Among these, lysis30 of TEG served as the only independent predictive marker (hazard ratio, 0.09; *P*=0.037) even after adjustment for INR and platelet count. In addition, maximum amplitude was significant factor for developing overt encephalopathy, but was not independent predictor. However, results of TEG did not show any significant association with other secondary outcomes.

Conclusions: In this study, we confirmed that TEG plays a major predictor for the occurrence of short-term major bleeding in patients with cirrhosis.

Keywords: Thromboelastography, Cirrhosis, Prognosis, Bleeding

OP-022

Validation of the Animal Naming Test in the Screening of Minimal Hepatic Encephalopathy

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Aims: Burden of minimal hepatic encephalopathy (MHE) is significant, but easy and valid tools for screening is an unmet need. We aimed to validate the animal naming test for MHE screening in Korea.

Methods: Liver cirrhosis (LC) patients without history of overt HE were recruited prospectively from 13 centers. All p articipants completed Korean paper-pencil test (KPPT) and the animal naming test (ANT). ANT consists of listing as many names of animals as possible in a minute. The number of animals listed in one minute (ANT1) was collected. MHE was diagnosed when KPPT scores ≥ 2.

Results: A total of 629 healthy controls and 124 LC patients were enrolled. The most common etiology of LC was alcohol (64.0%). Mean MELD score of LC patients was 11. Prevalence of MHE was 39.2% by KPPT. ANT1 was negatively correlated with age (ρ=-0.233, *P*<0.001) and positively correlated with education-years (ρ=0.298, *P*<0.001) in the healthy controls. ANT1 was significantly correlated with KPPT scores (ρ=-0.387, *P*<0.001) in LC patients. ANT1s were significantly different between healthy controls and LC patients (*P*<0.001). ANT1s for healthy controls, LC patients without MHE, and LC patients with MHE were 17.4±4.6, 16.9±5.1, and 13.1±3.7, respectively. They were different when compared between LC patients without MHE and LC patients with MHE (*P*<0.001). ANT1 (OR 0.713, *P*<0.001) was the only significant factor independent of model for end-stage liver disease (MELD) score in multivariate analysis for MHE diagnosis. The cut-off point for the highest Youden's index value was 15.5 for ANT1 with 77.6% of sensitivity and 57.3% of specificity.

Conclusions: The animal naming test is an easy, simple and valid method for screening of MHE.

Keywords: Minimal hepatic encephalopathy, Cirrhosis, Screening, Animal naming test

OP-023

Direct Bilirubin Is More Valuable for Predicting Prognosis in Patients with Liver Cirrhosis

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Aims: Most prediction models evaluating prognosis of patients with liver cirrhosis are based on serum total bilirubin level. However, because some patients with predominant indirect bilirubinemia have different predisposing factors from patients with direct bilirubinemia, direct bilirubin may have more beneficial role in predicting prognosis of cirrhotic patients.

Methods: Admitted patients clinically diagnosed with liver cirrhosis were enrolled. Patients with hepatocellular carcinoma or other malignancy were excluded. Six-month mortality was the primary outcome of this study.

Table 1. Baseline characteristics of total patients

	All pts (n=461)	Pts without 6-month mortality (n=375)	Pts with 6-month mortality (n=86)	*P*
Age	56.6 ± 12.0	56.7 ± 11.9	56.1 ± 12.6	0.674
FU duration	25.7 ± 21.1	31.3 ± 19.5	1.3 ± 1.4	<0.001
PLT	103.8 ± 60.8	104.9 ± 57.9	99.1 ± 72.4	0.422
INR	1.5 ± 0.6	1.4 ± 0.5	2.0 ± 0.7	<0.001
Albumin	3.2 ± 0.7	3.3 ± 0.7	2.7 ± 0.5	<0.001
TB	5.7 ± 8.0	3.7 ± 4.5	14.4 ± 12.7	<0.001
DB	3.0 ± 5.3	1.7 ± 2.8	8.7 ± 8.7	<0.001
ALT	83.2 ± 289.5	82.9 ± 315.0	84.4 ± 130.1	0.966
Cr	1.1 ± 0.8	1.0 ± 0.4	1.6 ± 1.6	<0.001
Na	135.9 ± 5.1	136.6 ± 4.4	133.1 ± 6.5	<0.001
Male	343 (74.4)	282 (75.2)	61 (70.9)	0.413
Etiology				0.050
Alcohol	251 (54.4)	196 (52.3)	179 (47.7)	
Other	210 (45.6)	55 (64.0)	31 (36.0)	
Hypertension	124 (26.9)	101 (26.9)	23 (26.7)	0.972
Diabetes	116 (25.2)	98 (26.1)	18 (20.9)	0.316
MELD	10.6 ± 3.2	9.7 ± 2.3	14.6 ± 3.4	<0.001
DB MELD	10.7 ± 3.2	9.8 ± 2.2	14.9 ± 3.6	<0.001

Results: In total, 461 cirrhotic patients were enrolled. Age was 56.6±12.0 years and 343 patients (74.4%) were men. Alcoholic liver disease was the most frequent underlying liver disease (251 patients, 54.4%). Model of End-stage Liver Disease (MELD) score was 10.6±3.2. Among 461 patients, 86 patients (18.7%) died within 6 months. International normalized ratio (INR), serum total bilirubin (TB), direct bilirubin (DB), creatinine levels, and MELD score were significantly higher, while serum sodium level was significantly lower in patients with 6-month mortality than in those without 6-month mortality. On multivariate analysis, INR, TB, DB, albumin, and creatinine were independent predictors for 6-months mortality. Area under the receiver operating characteristic curve (AUROC) of the DB for predicting 6-month mortality was 0.871 (95% CI, 0.834-0.908), and it was significantly higher than that of TB 0.852 (95% CI, 0.809-0.894) (*P*=0.005). AUROC of MELD score using TB for predicting 6-month mortality was 0.892 (95% CI, 0.860-0.919). While, AUROC of MELD score using DB for 6-month mortality was 0.899 (95% CI, 0.868-0.925), which was significantly higher than that of preexist MELD score (*P*=0.044).

Conclusions: Direct bilirubin is might be more worthy for predicting prognosis in patients with liver cirrhosis.

Keywords: Direct bilirubin, MELD score, Liver cirrhosis, Prognosis

OP-024

Impact of Relative Adrenal Insufficiency in Alcoholic Hepatitis (RAIAH)

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Background and Aims: Relative adrenal insufficiency (RAI) is frequently observed and associated with increased mortality in patients with liver cirrhosis. However, no clinically significant data about differences in the causes of cirrhosis have been reported. In particular, clinical data regarding RAI in patients with alcoholic hepatitis, where steroids are an important treatment, have rarely been reported. We investigated the prevalence and clinical significance of RAI in patients with alcoholic liver disease.
Method: This prospective observational study included 111 admitted patients with alcoholic hepatitis. The peak cortisol was defined as the highest cortisol concentration whether at 30 or 60 minutes after 250 mg synacthen injection. Delta cortisol was defined as the difference between the peak and basal cortisol levels. RAI was defined as a peak cortisol level < 18 mg/dL, basal cortisol level < 15 mg/dL or delta cortisol < 9 mg/dL.
Results: Among the 111 patients, most patients were male (79.3%) with a mean age of 54.5 ± 11 years and median modified discriminant function (mDF) score of 27.0 (interquartile range, 15.0–45.5). RAI was identified in 78 patients (70.3%). The basal level of cortisol in patients with RAI (13.7 ± 9.9 mg/dL) was significantly lower than in those without RAI (26.8 ± 13.7 mg/dL). A significant negative correlation was observed between the mDF score and delta cortisol level (γ = −0.281, *P*=0.003). Eight (10.2%) of 78 patients with RAI and two of 33 (6.0%) patients without RAI received corticosteroids. However, no significant differences were observed in overall survival or the steroid treatment response between patients with and without RAI (*P*>0.05).
Conclusion: Although no independent predictor of survival or the treatment response was observed for RAI, it was frequent in patients with alcoholic liver disease and was associated with the severity of alcoholic hepatitis.
Keywords: Alcoholic hepatitis, Relative adrenal insufficiency, Survival

[Group 5] June 21, 2019 | 15:30-16:30

HCV

OP-025

Regression of Liver Fibrosis Assessed by Transient Elastography after Daclatasvir and Asunaprevir Combined Treatment in Patients with Chronic Hepatitis C with Genotype 1b Infection: Prospective Cohort Study (RELIF-C)

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Aims: The development of directing acting antivirals (DAA) has made it easier to reach sustained virologic response (SVR) in patients with hepatitis C infection. However, it is not yet elucidated how much liver fibrosis get better by achievement of SVR after DAA treatment. Primary endpoint of this study is to evaluate the improvement of liver fibrosis by transient elastography (TE) after Daclatasvir/Asunaprevir (DCV+ASV) treatment.
Methods: Liver stiffness measurement using transient elastography as well as serum liver fibrosis scores [fibrosis-4 (FIB-4) score and the aspartate aminotransferase to platelet ratio index (APRI)] were evaluated at baseline and 48 weeks after starting DAA treatment. One hundred three patients with chronic hepatitis C Genotype 1b without resistance-associated substitution (RAS) mutation were enrolled in 9 tertiary medical centers. Patients with elevated liver enzyme (n=1) and who failed to follow-up (n=18) were excluded.
Results: Eighty four patients were eligible for this analysis. Mean age of patients was 68.1±9.7 years. Two patients failed to achieve SVR. Liver stiffness value after treatment with DAA was significantly decreased compared with baseline (15.0±11.0 vs. 19.8±12.4 kPa; *P*<0.001). Fibrosis stage assessed by TE was staged down significantly after DAA treatment (3.13±1.05 vs. 3.69±0.56, *P*<0.001) and 34 (40.5%) patients showed improvement in their fibrosis stage. Additionally, aspartate transaminase (31.0±23.5 vs. 65.2±37.2 IU/ml, *P*<0.001.) and alanine transaminase (30.4±38.6 vs. 43.9±38.6 IU/ml, *P*<0.001) was markedly decreased after DAA treatment. Reduction in FIB-4 score (5.59±3.93 vs. 3.52±4.03, *P*<0.001) and APRI score (0.74±1.14 vs. 1.37±1.05, *P*<0.001) were also observed. In univariate analysis, improvement in fibrosis stage was associated with age, baseline liver stiffness, body mass index (BMI), platelet level, albumin level, prothrombin time. Multivariate analysis, only lower BMI showed significance with improvement in liver stage (Odd ratio, Confidence interval; 0.483, 0.249-0.937, *P*=0.032).
Conclusions: Eradication of hepatitis C virus with DAA showed improvement in liver stiffness and serum fibrosis score. Long-term follow up will be needed for prove its clinical benefit.
Keywords: HCV, DAA, Transient elastography, Liver fibrosis

OP-026

SVR Following Treatment with Direct Acting Antiviral Regimens Is Durable in More than 6,600 Patients: The Gilead SVR Registry Study

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Aims: DAA therapy for HCV has provided the potential for large numbers of patients to achieve SVR raising the potential for elimination. While SVR rates are high in clinical studies and real world settings, it is important to demonstrate the durability of response. In addition, there are limited data regarding the long term outcomes of patients after achieving SVR with DAA therapy. Here we report the results of the Gilead SVR registry.

Methods: Patients were eligible for enrollment within 3 months of achieving SVR in a Gilead treatment study. Patients were followed with visits every 24 weeks for up to 144 weeks. At each visit, clinical assessment, HCV RNA measurements, and liver function tests were performed. For patients with virologic failure, sequencing and comparison with the pre-treatment baseline including phylogenetic analysis was performed differentiating relapse and reinfection.

Results: 6607 patients were enrolled. 1724 had received SOF+RBV±PEG, 2204 had received LDV/SOF±RBV, 1422 had received SOF/VEL±RBV, 597 had received SOF/VEL/VOX, and 660 had received other regimens. The majority of patients were male (62%), White (84%), non-cirrhotic (82%). Overall 99.3% of patients maintained SVR. Thirty patients experienced virologic failure of whom 8 (0.1%) had experienced relapse after completing their treatment study and 22 (0.3%) had reinfection. 232 patients experienced liver disease events, including HCC, which were most commonly observed in patients with advanced fibrosis. No patients with F0-F1 disease developed HCC; the exposure adjusted incident rates for HCC in patients with F2, F3, or F4 disease were 0.06%, 0.25%, and 0.58% respectively.

Conclusions: In this heterogeneous population SVR12 is confirmed as the optimal time to determine SVR as late relapses beyond this point are rare. In patients who achieve SVR, liver related complications are infrequent. These findings emphasize the value of SVR, regardless of fibrosis score at the time of treatment.

Keywords: SVR12, DAA, Durability, HCV

OP-027

Treatment with Sofosbuvir-Ledipasvir for Patients with HCV Genotype 2 Infection: A Real-World Experience of Six Hospitals in Taiwan

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Background: Sofosbuvir-ledipasvir has been proved to achieve high rate of sustained viral response for treatment of patients with HCV genotype 1 infection worldwide. As for patients with HCV genotype 2 infection, sofosbuvir combined with weight-based ribavirin was recommended based on earlier studies. However, the rate of sustained viral response was lower than 90% in several large cohorts. In Asia-Pacific region, the pooled analysis of three clinical studies in Taiwan, Japan and New Zeeland revealed that using sofosbuvir-ledipasvir for patients with HCV genotype 2 infection without decompensated cirrhosis could result in more than 95% of sustained viral response. Based on these results, sofosbuvir-ledipasvir has been reimbursed for treatment of patients with HCV genotype 2 infection since Oct 2018 in Taiwan.

Aim: The aim of our study is to evaluate the efficacy and safety of sofosbuvir-ledipasvir for patients with HCV genotype 2 infection.

Method: A total of 67 patients with HCV genotype 2 infection, who were treated by sofosbuvir-ledipasvir since Oct 2018, were enrolled from six hospitals in the middle-area of Taiwan. Baseline clinical characteristics, viral response, and serial changes of estimated glomerular filtration rate (eGFR) were assessed. Adverse effects were also recorded in this study.

Result: Among 67 patients, the mean age was 67.5±11.6 years old, 43 (64.2%) were female. 36 patients (53.7%) had history of cirrhosis and none of them had decompensation. Mean HCV RNA was 2.51 MIU/ml and 13 (19.4%) patients has mixed genotypic infection. The baseline ALT was 81 [15,389] IU/ml, platelet was 148.9±56.4 k/ul, and eGFR was 86±24.6 ml/min. There were 55 patients yet to achieve complete follow-up duration by Apr. 02, 2019. The rate of SVR 12 was 100% (12/12) for those patients with complete follow-up duration. Viral response in week 4 and end of treatment was 97% (65/67) and 100% (67/67), respectively. Serial eGFR in baseline, week 4 and end of treatment was 86, 83.8 and 86.2 ml/min respectively without significant change (p=0.146). Only 5 (7.4%) patients has mild adverse events and none discontinuity of treatment

due to intolerance.

Conclusion: For patients with HCV genotype 2 infection without decompensated cirrhosis, sofosbuvir-ledipasvir could provide good rate of sustained viral response up to 100% with limited side effects and no significant deterioration in eGFR level. The overall final rate of SVR12 would be updated recently and presented in Korea in Jun 2019.

OP-028

Substitution Mutations at Cys 316 of NS5B Affect Treatment with Sofosbuvir by Enhancing Replication of Genotype 1b Hepatitis C Virus

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Aims: Treatment of patients with chronic hepatitis C has been revolutionized by development of multiple direct-acting antivirals (DAAs). Most of DAAs target viral proteins such as NS3 protease, NS5A, and NS5B RNA-dependent RNA polymerase (RdRp) of hepatitis C virus (HCV). Sofosbuvir is an antiviral drug targeting NS5B RdRp as a nucleotide analog and it is very potent and safe regarding antiviral resistance. However, potential resistance-associated substitutions (RASs) in NS5B are being reported after treatment failures.

Methods: We collected blood samples from the patients who failed in ledipasvir plus sofosbuvir (Harvoni) treatment. After isolation of viral RNAs and RT-PCR, the sequences of both NS5A and NS5B were determined by population sequencing method. Potential RASs of NS5B were introduced in the genotype 1a and 1b HCV replicon by site-directed mutagenesis and the effect of those mutations on viral RNA replication was assessed in the presence of varying concentrations of sofosbuvir.

Results: Sequencing analysis identified potential RASs of both NS5A and NS5B including L159F, C316N and A207T of NS5B. Subsequent in vitro analyses using the mutant HCV replicons showed that substitutions of potential RASs in NS5B did not change the half maximal effective concentration (EC_{50}) of sofosbuvir of mutant replicons compared to that of wild-type replicon but that some mutations including C316N enhanced viral RNA replication in a genotype-dependent manner.

Conclusions: These results suggest that the genotype-dependent enhancement of viral RNA replication by the mutations in NS5B may increase the chance of failure of the sofosbuvir-containing DAA therapies.

Keywords: hepatitis C virus, NS5B, Sofosbuvir, Resistance-associated substitution

OP-029

Efficacy and Safety of 8-Weeks of Glecaprevir/Pibrentasvir in Treatment-Naïve Adults with HCV Genotype 1-6 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 1

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Aims: Aspartate aminotransferase to platelet ratio index (APRI) is a low-cost, widely available, non-invasive method to assess liver disease severity. Current EASL and WHO treatment guidelines recommend APRI as an option in low- to middle-income countries and non-specialty clinics to simplify HCV management. APRI ≤1 has a high negative predictive value (98%) for cirrhosis compared to liver biopsy, establishing an attractive threshold to exclude liver cirrhosis. Here, we report preliminary data from the first prospective Phase 3 trial to use APRI to select patients for an 8-week treatment with the fixed-dose, pangenotypic, direct-acting antiviral combination of glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor) coformulated as G/P.

Methods: This prospective, single arm Phase 3 trial with 43 sites worldwide (NCT03212521) aims to evaluate the efficacy and safety of G/P (300/120mg) QD administered for 8 weeks in treatment-naïve adults with chronic HCV genotypes (GT) 1-6 infection and APRI ≤1. Efficacy is assessed using intent-to-treat (ITT) and modified ITT analyses as the percentage of patients who received ≥1 dose of G/P and achieved sustained virologic response at post-treatment week 12 (SVR12). Safety is assessed in all patients treated with ≥1 dose of G/P.

Results: Of the 230 patients enrolled, the median APRI score was 0.41 (range from 0.13 to 1.00). Patients (n, %) were primarily white (207, 90%), <65 years of age (207, 90%), and had an APRI score ≤0.5 (140, 61%). Notably, 35 (15%) patients had GT3 infection, while most others had GT1 infection (151, 66%). For all patients who completed treatment (on G/P for ≥52 days), those with available post-treatment week 4 and 12 HCV RNA data (Figure) all achieved SVR4 (221/221) and SVR12 (61/61). Two patients who discontinued G/P early did not achieve SVR. Headache (13%) was the only adverse event (AE) reported in ≥10% of patients. AEs leading to G/P discon-

tinuation and serious AEs were reported in 2 (<1%) and 4 (2%) patients, respectively. Post-treatment follow-up is currently ongoing. There are no virologic failures to date. Complete efficacy and safety data will be presented at the Congress.

Conclusions: Preliminary data suggests that 8-week G/P treatment is highly efficacious and safe in HCV treatment-naïve patients with chronic HCV infection and APRI ≤1. These results support the use of this APRI threshold as an acceptable patient selection criterion to aid strategies for HCV elimination or treatment of patients in a primary care setting.

Keywords: Hepatitis C, Liver cirrhosis, Blood platelet

OP-030

Efficacy and Safety of Grazoprevir/Elbasvir for Korean Patients with Chronic Hepatitis C Virus Infection: A Retrospective, Nationwide, Real-World Study

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Aims: Grazoprevir/elbasvir had been accepted as a reimbursable treatment regimen by Korean National Health Insurance for genotype 1 or 4 chronic hepatitis C patients since May 2017 in Korea. This study aimed to clarify a real-world efficacy and safety of grazoprevir/elbasvir therapy in South Korea.

Methods: A total of 242 patients with chronic HCV infection who started grazoprevir/elbasvir were consecutively enrolled from 7 tertiary hospitals during May 2017 ~ Jun 2018. Retrospective analysis on the sustained virological response (SVR), and adverse events was performed.

Results: Mean age of enrolled patients was 59.0 ± 12.6 yeard old and 47.5% were males. Hypertension was most common (72, 29.8%) comorbid disease, following by diabetes (55, 22.7%) and chronic kidney disease (16, 6.6%). Since 29 subjects were lost to follow up before SVR evaluation, SVR rates were 85.5% (182/213) in treatment-naïve and 93.1% (27/29) in treatment-experienced patients as intention-to-treat analyses, and those were 97.8% (179/183) in treatment-naïve and 100% (28/28) treatment-experienced patients as per-protocol analyses. Any grade of adverse events had been reported in 51 (21.1%) of treated patients. Itching (29, 12%), liver function test abnormality (11, 4.6%) and fatigue (2.9%) were common adverse events. Of 4 patients who discontinued the antiviral therapy, 3 had experienced mild adverse events (1 fatigue, 1 headache, and 1 liver enzyme abnormality) but all treatment withdrawals were based on patient's willingness, not by physician's decision for the adverse events.

Conclusions: Grazoprevir/elbasvir showed high real-life efficacy and safety in Korean patients with chronic HCV infection regardless of previous antiviral treatment experience.

Keywords: Hepatitis C virus, Grazoprevir, Elbasvir, Real-world study, Korea

[Group 6] June 21, 2019 | 15:30-16:30

Others

OP-031

Identification of Liver Injury by Fimasartan, a Novel Angiotensin II Receptor Blocker: Analysis of National Health Insurance Service Data

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Aims: Fimasartan, one of major antihypertensive agent in Korea, has been sporadically reported as a possible cause of severe drug-induced liver injury (DILI) since it was approved by Korea Food and Drug Administration in 2010. We performed a large-scale cohort study to identify association between fimasartan use and admission with liver-related diseases.

Methods: From 2010 to 2017, treatment-naïve patients who were prescribed fimasartan, candesartan, or valsartan were collected from the customized data of the National Health Insurance Service in Korea. Patients with cumulative daily drug dosage less than 56 days, age < 20 years or > 80 years, and missing demographic data were excluded. Candesartan and valsartan were selected as control groups and compared with fimasartan. The primary outcome was any admission with liver-related diseases and the secondary outcome was overall mortality. Liver-related diseases were defined as treatments with one of following disease codes, toxic liver disease (K71), hepatic failure (K72), non-specific reactive hepatitis (K75.2), inflammatory liver disease (K75.9), unspecified liver disease (K76.9).

Results: A total of 49,726 patients were enrolled. Mean age was 57.6 years and females were 38.3% of them. Of patients with candesartan (N=22,238), valsartan (N=21,016), and fimasartan (N=6,472), admissions with any liver-related diseases

were 2,197 (9.88%), 1,928 (9.17%), and 579 (8.95%), respectively. The admission rate was 22.3 / 1,000 person-year, 20.1 / 1,000 person-year, and 26.6 / 1,000 person-year for candesartan, valsartan, and fimasartan group, respectively. Multivariate analysis after adjusting age, gender, income level, residence area, and comorbidity showed that fimasartan was associated with higher risk for admission than control (candesartan and valsartan) (hazard risk, 1.258; 95% confidence interval, 1.152–1.374; *P*<0.0001). However, risk for overall mortality didn't differ between two groups.

Conclusions: Fimasartan might have a higher risk for hepatotoxicity than the same class of anti-hypertensive agents in treatment-naïve patients. When caring patients with unknown liver injury, fimasartan-induced hepatotoxicity should be considered.

Keywords: Angiotensin II type 2 receptor blockers, Drug-induced liver injury, Fimasartan

OP-032

Clinical Indication and Safety of Liver Biopsy in the Era of Noninvasive Assessment of Liver Fibrosis

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Aims: Liver biopsy (LB) remains the gold standard for evaluation of liver disease. However, during the past two decades, many noninvasive tests have been developed and utilized in clinical practice to replace LB. The aim of this study is to evaluate clinical use and its safety of LB in the era of noninvasive assessment of liver fibrosis.

Methods: This retrospective study included consecutive 1945 LB cases between 2001 to 2018 in a tertiary hospital. All the LB was undertaken in ultrasound-guided with 18 gauge cutting needles. Indications of LB and adverse events (AEs) of each patient were collected.

Results: LB was performed approximately 108 times a year on average during this period. However, the number of LBs tended to decrease after 2008, when transient elastography was introduced in the institution. Chronic hepatitis B was the most common indications for LB (25.4%), followed by liver mass (19.9%), abnormal liver Tests of unclear Etiology (18.5%), and nonalcoholic fatty liver disease (NAFLD) (13.1%), respectively. When classified by period, NAFLD has increased from 10.9 to 17.5% in the last 5 years compared to the last 10 years, and viral hepatitis decreased from 30.7% to 19.3%. The overall rate of major AEs was 0.05% (1 case), presented with biopsy site bleeding. Liver cirrhosis was observed in 563 cases (28.9%), and none of them experienced major AEs.

Conclusions: LB is widely used in clinical practice as an irreplaceable diagnostic tool even in the era of noninvasiveness. Also, ultrasound-guided method can be performed safely in patients with liver cirrhosis.

Keywords: Liver biopsy, Indication, Complication, Safety

OP-033

Plasma Levels of Soluble Programmed Death-1 and Programmed Death-Ligand 1 in the Patients with Autoimmune Hepatitis and Primary Biliary Cholangitis

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Aims: While tissue expression of programmed death-1 (PD-1)/PD-ligand 1 (PD-L1) was reported in autoimmune hepatitis (AIH), the profiles of plasma levels of soluble PD-1 (sPD-1) and soluble PD-L1 (sPD-L1) in AIH and primary biliary cholangitis (PBC) were not reported. This study aimed to investigate the implication of sPD-1 and sPD-L1 in AIH and PBC.

Methods: Using plasma samples obtained from the prospectively enrolled patients with AIH (n=43), PBC (n=80), and AIH-PBC variant (n=8), and age-and sex-matched healthy controls (n=57), the plasma levels of sPD-1 and sPD-L1 were measured by commercial ELISA.

Results: The mean age and female proportion (%) in AIH, PBC, AIH-PBC variant, and healthy controls was 61 years (81.4%), 56 years (86.3%), 54 years (100%) and 59 years (87.7%), respectively. The plasm sPD-1 was detected in 34.9%, 36.3%, 62.5%, and 31.6% of the patients with AIH, PBC, AIH-PBC variant, and healthy controls, respectively (*P*=0.40). The median plasma level of sPD-1 in either AIH PBC patients were not significantly different from healthy controls. The plasma sPD-L1 was detected in almost all the subjects. Compared to the median plasma sPD-L1 level in healthy controls (438 pg/mL), it was significantly higher in AIH patients (574 pg/mL) (*P*=0.001), but lower in PBC patients (191 pg/mL) (*P*=0.001). Moreover, plasma sPD-L1 level was significantly correlated with immunoglobulin G level (IgG) in AIH patients and with total bilirubin level in PBC patients.

Conclusions: Compared to healthy controls, the plasma level of sPD-L1 was higher in AIH with a significant correlation with IgG, while it was lower in PBC with a significant correlation with total bilirubin level.

Keywords: Soluble programmed death-1, Soluble programmed death ligand-1, Primary biliary cholangitis, Autoimmune hepatitis, Biomarker

OP-034

Clinical Characteristics of Liver Cirrhosis and Hepatocellular Carcinoma Occurring after Fontan Operation

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Aims: The most serious late post-Fontan complications are liver cirrhosis and hepatocellular carcinoma (HCC). The aims of this study were to investigate the cumulative incidence of cirrhosis and HCC and to identify specific features distinguishing HCC from benign arterial phase hyper-enhancing (APHE) nodules that developed after the Fontan operation.

Methods: We retrospectively enrolled 265 post-Fontan patients who had been followed for more than 5 years and had undergone ultrasound or computed tomography (CT) of the liver between 2000 and 2018. Cirrhosis was diagnosed by imaging features.

Results: During the 5103.2 person-years follow-up, the estimated cumulative incidence rates of cirrhosis at 5-, 10-, 20-, and 30-years after the Fontan operation were 2.6%, 10.8%, 57.1%, and 98.3%, respectively (Figure 1). On multiphasic CT, 17 patients had APHE nodules ≥ 1 cm showing washout in the portal venous phase (PVP)/delayed phase which met current non-invasive HCC diagnosis criteria. Among them, only six patients (35.3%, 6/17) were diagnosed with HCC. Thus, the annual incidence of HCC was 0.1% during 5097.7 person-years of follow-up after the Fontan operation. After cirrhosis developed, the annual incidence of HCC was greater: 1.1% (6 HCCs/564.7 person-years). The appearance of washout in the PVP (P=0.01) and the serum AFP level (P<0.001) were significantly associated with HCC among the APHE nodules.

Conclusions: In post-Fontan patients, cirrhosis is a frequent late complication, especially after 10 years. Diagnosis of HCC should not be based solely on the current imaging criteria, and presence of washout on PVP and high serum AFP might be helpful to differentiate HCC nodules from benign APHE nodules.

Keywords: Fontan-associated liver disease, Arterial phase hyper-enhancing nodules, Congestive hepatopathy, Congenital heart disease

OP-035

The Validity of Two-Dimensional Shear Wave Ultrasound for Assessing Fibrosis Stage in Patients with Chronic Liver Disease: Comparison with Transient Elastography

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Aims: Compared to transient elastography (fibroscan), two-dimensional shear wave elastography (2D-SWE) has the advantage of performing simultaneous ultrasonographic examination and measuring liver stiffness at the same time. However, the diagnostic performance and clinical usefulness of 2D-SWE are not fully validated. In this study, we evaluated whether newly developed 2D-SWE (RS85, Samsung-shearwave imaging) is valid and reliable for predicting liver fibrosis stage when compared with fibroscan.

Methods: We prospectively enrolled 117 patients with chronic liver disease. 2D-SWE, fibroscan, laboratory test and liver biopsy were performed on a same day from two tertiary care hospital. One patient who had unreliable measurement was excluded. The measurement of 2D-SWE was considered acceptable when homogenous color pattern in a region of interest of at least 10 mm was shown at 10 different sites. Diagnostic performance was calculated using area under the receiver operating characteristics curve (AUROC).

Fibrosis stage	THR†	SEN	SPE	AUC (95% CI)	Comparison of AUC
≥F2 vs. others					
2D-SWE (kPa)	≥5.8	88.9%	74.4%	0.851 (0.773-0.911)	P=0.79
Fibroscan (kPa)	≥5.7	93.1%	69.8%	0.859 (0.781-0.916)	
≥F3 vs. others					
2D-SWE (kPa)	≥7.5	95.4	81.7	0.917 (0.851-0.960)	P=0.14
Fibroscan (kPa)	≥7.2	95.4	67.6	0.881 (0.807-0.934)	
F4 vs. others					
2D-SWE (kPa)	≥9.4	95.0	82.1	0.889 (0.817-0.940)	P=0.08
Fibroscan (kPa)	≥10.4	95.0	81.1	0.938 (0.877-0.974)	

Results: Sixty three (54%) patients were male. Most common etiology of chronic liver disease was chronic hepatitis B (22%)

and followed by fatty liver disease (20%). Liver fibrosis stage consisted of F0 (18%), F1 (19%), F2 (24%), F3 (22%) and F4 (17%). Overall, 2D-SWE was well correlated with histologic fibrosis stage (r=0.601, *P*<0.001). For the diagnosis of significant fibrosis (≥F2), 2D-SWE showed good diagnostic ability (AUROC : 0.85, 95% confidence interval [CI], 0.773-0.911) as well as fibroscan (AUROC : 0.859, 95% CI : 0.781-0.916). The cut-off value of 2D-SWE for distinguishing significant fibrosis was 5.8 kPa. For the diagnosis of liver cirrhosis, AUROCs and optimal cut-off of 2D-SWE were 0.889 (95% confidence interval [CI], 0.817-0.940) and 9.4 kPa. Fibroscan showed slightly improved diagnostic performance in distinguishing cirrhosis,(AUROC : 0.938, 95% CI : 0.877-0.974), but there was no statistical significance (*P*=0.08 by deLong method).

Conclusions: Two-dimensional SWE has similar capabilities to fibroscan in diagnosing significant fibrosis and liver cirrhosis.

Keywords: 2D-SWE, Fibrosis, Shear wave elastography, RS85

OP-036

Proposal of a Cutoff for the Computed Tomography-Assessed Lumbar Skeletal Muscle Index for Diagnosing Sarcopenia in Asian Populations

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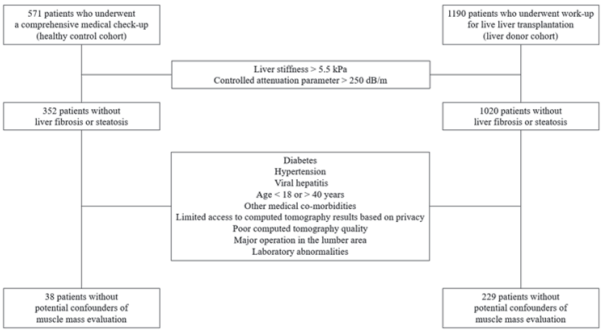
Aims: Criteria for defining sarcopenia have not been fully established. We proposed a new cutoff for the computed tomography-based skeletal muscle index (LSMI) for diagnosing sarcopenia

Methods: Subjects who underwent comprehensive medical check-ups and those who underwent screening for live liver donation were recruited. Skeletal muscle mass was assessed using computed tomography at the L3 level and the skeletal muscle area normalized to height squared (cm^2/m^2) for calculating the adjusted LSMI. The cutoffs for diagnosing sarcopenia were calculated as the means minus two standard deviations.

Results: A total of 267 subjects (38 who underwent health check-ups and 229 liver donors) were selected. The mean ages and LSMIs of the study population (145 males and 122 females) were 28.9 years and 48.0 cm^2/m^2, respectively. The LSMI was significantly higher in males than females (mean, 54.4 vs. 40.4 cm^2/m^2, *P*<0.001) and significantly decreased with age (50.95 cm^2/m^2 in those aged <26 years; 47.40 cm^2/m^2 in those aged 26–30 years; 46.62 cm^2/m^2 in those aged 31–35 years; 44.99 cm^2/m^2 in those aged 36–40 years, *P*=0.001). The lumbar skeletal muscle area was positively correlated with body mass index, aspartate and alanine transferase, serum albumin, gamma-glutamyl transpeptidase, serum creatinine, and triglycerides, whereas it was negatively correlated with age, female gender, platelet count, and high-density lipoprotein cholesterol level (all *P*<0.05). The cutoff for LSMIs for diagnosing sarcopenia were 40.0 and 30.0 cm^2/m^2 for males and females, respectively.

Figure 1. Flowchart of subject enrolment in the study population.



Among the 1,761 subjects, 342 subjects were excluded because of elevated liver stiffness and fatty liver, which might influence skeletal muscle mass. 1,152 subjects were further selected according to our exclusion criteria. Finally, 2670 subjects without potential confounders of skeletal muscle mass were selected for the statistical analysis.

Conclusions: We proposed a cutoff for computed tomography-assessed LSMI criteria, optimized for use in Asian populations.

Keywords: Sarcopenia, Lumbar skeletal muscle index, L3 level

[Group 7] June 21, 2019 | 15:30-16:30

HBV & Others

OP-037

Treatment Response of Noninvasive Fibrosis Markers Predicts Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients

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Aims: Potent antiviral therapy can regress hepatic fibrosis in chronic hepatitis B patients. Non-invasive fibrosis markers such as FIB-4, APRI, and fibroscan can assess the degree of fibrosis. This study evaluated the association between treatment responses of these markers and development of HCC.

Methods: This is a single center retrospective study enrolling 2,037 patients given antiviral agents (Entecavir or Tenofovir) from April 2005 to December 2017. FIB-4 and APRI were serially assessed from the start of the treatment and their values at 6 months and at 1year intervals for up to 8 years. Fibroscan were analyzed as well.

Results: Patients' median age was 48 years, 61% were male, and 33% had cirrhosis. During the follow-up period, HCC de-

veloped in 131 patients and median time to its occurrence was 56.9 months. Median values of FIB-4, APRI at baseline were 1.9, and 1.0, respectively. Patients were divided into four groups by the fibrosis regression at 12 months after treatment initiation (Table 1). The risk of HCC development in group 1 was significantly lower than that in group 2 or 4, but not in group 3 (P<0.001, Figure 1). In hepatitis patients, univariate analysis revealed that age (≥60 years), BMI (≥23), and FIB-4 response (Group 2,4) were significantly associated with HCC development. Multivariate analysis identified a lack of improvement of FIB4 (OR 4.93; 95% CI 1.74-14.00; P=0.003), and BMI (OR 2.69; 95% CI 1.12-6.43; P=0.026) to be independent prognostic factor for HCC development. In cirrhosis patients, age (≥60 years), sex (male), Child-Pugh score (>5), alpha-fetoprotein level (≥10 ng/mL), and fibrosis response (Group 2,4) were significantly associated with HCC development. Multivariate analysis demonstrated age (OR 2.79; 95% CI 1.73-4.49; P<0.001), sex (OR 2.20; 95% CI 1.39-3.49; P=0.001), and lack of improvement of APRI (OR 2.26; 95% CI 1.10-4.63 P=0.027) to be significantly associated with the development of HCC.

Patient groups by the response of noninvasive fibrosis markers during antiviral treatment; baseline and at 12 months after treatment initiation.

FIB-4	Baseline	Follow-up
Group1	<3.25	<1.45
Group2	<3.25	≥1.45
Group3	≥3.25	<1.45
Group4	≥3.25	≥1.45
APRI	Baseline	Follow-up
Group1	<1.5	<0.5
Group2	<1.5	≥0.5
Group3	≥1.5	<0.5
Group4	≥1.5	≥0.5

Conclusions: Our data suggests the clinical utility of serial assessment of non-invasive fibrosis markers during anti-HBV therapy. On-therapy liver fibrosis regression is an independent favorable indicator of HCC risk in patients with chronic HBV infection.

Keywords: Chronic hepatitis B, FIB-4, APRI, Hepatocellular carcinoma

OP-038

Anti-HBc IgG Level in Prediction of HBsAg Seroclearance in Chronic Hepatitis B Patients with Nucleos(t)ide Analogue induced HBeAg Seroclearance

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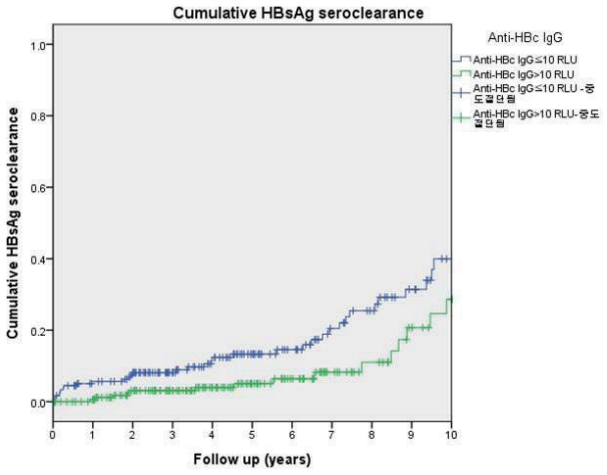
Aims: Although hepatitis B core antibody is outdated marker using enzyme immunoassay, the indirect ratio of light absorbance of anti-HBc IgG can be easily measured. We investigated whether the indirect ratio of anti-HBc IgG can predict HBsAg seroclearance among patients with nucleos(t)ide analogue induced HBeAg Seroclearance.

Methods: We performed a retrospective study from two tertiary hospital. A total of 355 chronic hepatitis B patients were included for analysis from Jan. 2008 to Dec. 2016. They were HBsAg seropositive, and experienced nucleos(t)ide analogue (entecavir, or tenofovir) induced HBeAg seroclearance. The indirect ratio of light absorbance of anti-HBc IgG levels was measured with chemiluminescent microparticle immunoassay using Architect Anti-HBc assay (Abbott Laboratories, IL, USA) before HBeAg seroclearance. We calculated cumulative incidences of HBsAg seroclearance. Association between level of anti-HBc IgG and HBsAg seroclearance were estimated by Cox proportional hazard regression.



Results: After 10-year follow-up period, 59 patients experienced HBsAg seroclearance (16%). Higher proportions of 181 patients with the indirect ratio of light absorbance of anti-HBc ≤10 (RLU, relative light unit) had HBsAg seroclearance (n=39, 21.5%) than 185 patients with higher levels of anti-HBc > 10 RLU (n=20, 10.8%) (P=0.005). For patients with levels of anti-HBc ≤10 RLU, the relative risk of HBsAg seroclearance was 1.70 (95% CI, 0.985–2.925), compared to patients with higher levels of anti-HBc (P=0.057).

Conclusions: Even if current diagnostic tool of anti-HBc IgG level is the indirect method, levels of anti-HBc ≤10 RLU were associated with HBsAg seroclearance within 10 years among patients with nucleos(t)ide analogue induced HBeAg Seroclearance. New quantification techniques of anti-HBc IgG are needed to verify these results.

Keywords: Anti-HBc, HBsAg seroclearance, HBeAg seroclearance, Chronic hepatitis B

OP-039

Maximal Diameter of Hepatic Abscess Independently Predicts Prolonged Hospitalization and Poor Prognosis in Patients with Pyogenic Liver Abscess

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Aims: The aim of this study was to investigate the factors associated with prolonged hospital stay and in-hospital mortality in pyogenic liver abscess patients.

Methods: We retrospectively reviewed data from pyogenic liver abscess patients who were admitted from 2005 to 2018 at Chonbuk University Hospital. Patients were categorized into 3 groups by maximal diameter of the abscess (< 5 cm, 5-10 cm, ≥ 10 cm) and compared clinical characteristics. Prolonged hospital stay was defined as hospitalization more than 14 days.

Results: A total of 482 patients (301 men and 181 women) diagnosed with pyogenic liver abscess were enrolled for the study. The patients had a mean age of 64.4 ± 14.6 years and approximately one fourth of patients had underlying diabetes mellitus, hypertension, and biliary disease, respectively. Mean maximal diameter of hepatic abscess was 5.7 ± 2.6 cm and 76.4% was single lesion. Culture positive rate of microorganism isolated from blood or pus was 40.5% and *Klebsiella pneumoniae* species accounted for 71.9% of total isolated microorganisms. Although there was no difference in the underlying disease or vital sign at admission, laboratory parameters indicating inflammation deteriorated with increasing size. Admission duration and in-hospital mortality were higher in the large hepatic abscess group. Next, we analyzed factors related to long-term hospitalization. Multivariate analysis revealed high baseline hsCRP and procalcitonin levels and large maximal abscess diameter were independent factors associated with prolonged hospital stay. Regarding 30-day mortality, there were 11 expired cases (3.1%) during the period. In multivariate analysis, decreased mentality at admission, baseline hemoglobin level less than 9 mg/dL, and maximal diameter of abscess were independent factors associated with 30-day mortality.

Conclusions: Large maximal diameter of liver abscess at admission indicated prolonged hospitalization and poor prognosis. More aggressive treatment strategies with careful monitoring may be required in patients with large liver abscess.

Keywords: Liver abscess, Pyogenic, Hospitalization, Hospital Mortality

Table 1. Factors associated with prolonged hospital stay (> 14 days)

	Univariate analysis				Multivariate analysis			
	P value	HR	Lower CI	Upper CI	P value	HR	Lower CI	Upper CI
Age ≥ 65 years, vs <65	0.1622	1.31	0.90	1.91				
Male sex	0.6927	0.92	0.63	1.36				
Malignancy	**0.0376**	**2.00**	**1.07**	**3.98**	0.1256	5.54	0.88	109.19
Biliary disease	0.3741	0.83	0.54	1.26				
DM	**0.0017**	**2.03**	**1.31**	**3.18**				
HTN	0.0543	1.56	1.00	2.48				
Chronic liver disease	0.1774	0.49	0.17	1.39				
Previous liver abscess history	0.1415	0.34	0.07	1.40				
Significant alcohol consumption	0.5771	0.83	0.44	1.61				
Decreased mentality at admission	0.4059	0.55	0.13	2.37				
Shock at admission	0.1101	1.64	0.91	3.10				
WBC ≥ 12,000 /mm³, at baseline	**0.0003**	**2.01**	**1.38**	**2.95**	0.0681	2.31	0.95	5.79
Hb < 9 mg/dL, at baseline	0.3099	1.51	0.70	3.52				
Na < 135 mmol/L, at baseline	0.5926	1.11	0.76	1.62				
ALT ≥ 200 IU/L, at baseline	0.3727	1.44	0.67	3.36				
hsCRP ≥ 200 mg/L, at baseline	**0.0054**	**1.83**	**1.20**	**2.83**	**0.0254**	**3.30**	**1.21**	**10.11**
PCT ≥ 5 ng/mL, at baseline	**0.0001**	**3.54**	**1.90**	**6.82**	**0.0094**	**3.67**	**1.41**	**10.14**
Number of abscess, single vs multiple	0.4080	1.21	0.78	1.91				
Maximal abscess diameter (< 5 cm, 5-10 cm, ≥ 10 cm)-	**0.0006**	**1.98**	**1.35**	**2.95**	**0.0262**	**2.40**	**1.14**	**5.42**
PCD insertion during admission	**0.0058**	**1.70**	**1.17**	**2.49**				
PCD insertion within 3 days of admission	**0.0111**	**0.42**	**0.20**	**0.80**				
Culture positive (blood or pus)	**0.0007**	**1.98**	**1.34**	**2.95**				

DM, diabetes mellitus; HTN, hypertension; WBC, white blood cells; Hb, hemoglobin; hsCRP, high sensitivity C-reactive protein; PCT, procalcitonin; PCD, percutaneous catheter drainage

Table 2. Factors associated with 30-day mortality

	Univariate analysis				Multivariate analysis			
	P value	HR	Lower CI	Upper CI	P value	HR	Lower CI	Upper CI
Age ≥ 65 years, vs <65	**0.0495**	**7.99**	**1.48**	**147.97**	0.1064	6.15	0.96	122.85
Male sex	0.6198	1.41	0.39	6.62				
Malignancy	0.4409	1.86	0.28	7.64				
Biliary disease	0.1075	2.81	0.77	10.25				
DM	0.2148	0.27	0.01	1.45				
HTN	0.3048	0.34	0.02	1.82				
Chronic liver disease	0.9930							
Previous liver abscess history	0.9922							
Significant alcohol consumption	0.9924							
Decreased mentality at admission	**0.0027**	**13.47**	**1.84**	**65.53**	**0.0034**	**39.09**	**3.13**	**533.91**
Shock at admission	0.1663	2.65	0.56	9.81				
WBC ≥ 12,000 /mm³, at baseline	0.1319	3.32	0.82	22.14				
Hb < 9 mg/dL, at baseline	**0.0114**	**6.10**	**1.27**	**23.13**	**0.0280**	**7.43**	**1.16**	**47.61**
hsCRP ≥ 200 mg/L, at baseline	**0.0369**	**4.44**	**1.15**	**21.26**	0.1274	3.57	0.75	21.91
PCT ≥ 5 ng/mL, at baseline	0.9948							
Number of abscess, single vs multiple	0.2855	2.01	0.51	7.17				
Maximal abscess diameter (< 5 cm, 5-10 cm, ≥ 10 cm)	**0.0092**	**3.85**	**1.42**	**11.05**	**0.0090**	**5.96**	**1.64**	**24.86**
PCD insertion during admission	0.9050	0.93	0.25	3.37				
PCD insertion within 3 days of admissi	0.6766	1.60	0.23	31.59				
Culture positive (blood or pus)	0.2011	0.36	0.05	1.46				

DM, diabetes mellitus; HTN, hypertension; WBC, white blood cells; Hb, hemoglobin; hsCRP, high sensitivity C-reactive protein; PCT, procalcitonin; PCD, percutaneous catheter drainage

OP-040

Comparative Analysis of Intrahepatic Infiltration of Activated T Cells and Macrophages between Autoimmune Hepatitis and Drug-Induced Liver Injury

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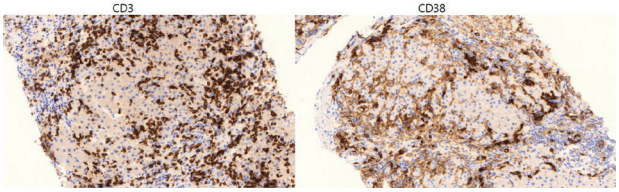
Aims: Pathogenesis of autoimmune hepatitis (AIH) involves genetic susceptibilities, molecular mimicry events, and dysfunction of immunoregulatory mechanisms. The major immune characteristic of AIH is the presence of a marked CD4 and CD8 T-cell infiltrate involved in hepatocellular damage. In this study, we aimed to identify the amount and patterns of immune cell infiltration in AIH, and to compare them with those of drug-induced liver injury (DILI).

Methods: From March 2016 to December 2018, 15 patients with AIH were prospectively enrolled in this study. For comparison, 22 patients with DILI in the same period were analyzed in the same way. Liver biopsy was performed, and immunohistochemical stain for CD3, CD68, CD20, and CD38 was done. Experienced pathologist confirmed the pathologic and immunohistochemical findings. For some patients, immune cells were harvested from fresh liver biopsy samples, and multicolor flow cytometry was used for the immunophenotyping of the infiltrated immune cells.

Results: First, we identified that activated CD8 and CD4 T cells were more infiltrated in the livers from patients with AIH than those from healthy controls by multicolor flow cytometry. Next, the frequency of infiltrated T cells, macrophages, and B cells were quantified by immunohistochemistry. The amounts of T cells, macrophages, and B cells infiltration had no associations with serum AST, ALT ALP or GGT in patients with AIH. Furthermore, serum levels of IgG and IgA were not correlated with the amounts of immune cells infiltrations, either. Next, we compared the infiltration of the immune cell subsets between patients with AIH and those with DILI. Baseline serum ALT was significantly higher in patients with DILI, but the levels of activated T cells (CD3+CD38+) infiltration were not significantly different between AIH and DILI. However, a larger number of macrophages were infiltrated in the livers in DILI than those in AIH, suggesting that drug-induced injury of hepatocytes triggers innate immunity more vigorously.



Conclusions: Both patients with AIH and DILI have activated T cells and macrophages infiltrated in the injured liver. Higher ALT and more macrophages infiltration in DILI suggest that drug-induced injury of hepatocytes might trigger innate immunity more vigorously than autoimmunity-mediated mechanisms.

Keywords: Autoimmune hepatitis, Drug-induced liver injury, T cell, Macrophage

OP-041

Positive Rate of Anti-Mitochondrial M2 Antibody and Anti-Soluble Liver Antigen Antibody in the Patients with Primary Biliary Cholangitis and Autoimmune Hepatitis in South Korea

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Aims: The anti-mitochondrial antibodies (AMA) detected by indirect immunofluorescence is the signature antibody for the diagnosis of primary biliary cholangitis (PBC). However, the anti-mitochondrial M2 antibody (AMA-M2) detected by ELISA is easy to measure with technical consistency. Anti-soluble liver antigen (SLA) antibody is detected in autoimmune hepatitis (AIH) reflecting a disease severity. There was little study on the AMA-M2 and anti-SLA in the patients with autoimmune liver diseases in South Korea. This study aimed to investigate the positive rate of AMA-M2 and anti-SLA in the patients with PBC and AIH with comparative analysis according to the positivity for AMA-M2 or for anti-SLA.

Methods: Using plasma samples obtained from prospectively enrolled patients with PBC (n=80), AIH (n=43), and AIH-PBC variant (n=8), and age-sex matched healthy controls (n=50) in registry in a tertiary hospital, presence of AMA-M2 and anti-SLA was determined by commercial ELISA kit (EUROIMMUN, Luebeck, Germany). Clinical data obtained from medical record were analysed.

Results: The positive rate of AMA-M2 was 83.8%, 14%, 50%, and 2% in PBC, AIH, AIH-PBC variant syndrome and healthy controls, respectively. There was no significant difference in laboratory findings between the AMA-M2 positive and negative group of PBC, and of AIH patients. In PBC patients, the sensitivity and specificity of AMA-M2 were 83.8% and 98% respectively. Moreover, AMA-M2 was positive in 4 patients with AMA negative PBC, while AMA was positive in 5 of AMA-M2 negative PBC. Anti-SLA was detected only in AIH group with positive rate of 7% (n=3). The anti-SLA positive patients showed a younger mean age (43 years) than the negative group (63 year) (P=0.335), otherwise, there was no significant difference in the clinical and laboratory findings between anti-SLA positive and anti-SLA negative group in AIH.

Conclusions: The AMA-M2 testing may be complementary for the diagnosis of AMA negative PBC, and the significance of anti-SLA in AIH should be studied further with a larger sample size.

Keywords: Anti-mitochondrial antibody M2 subtype, Anti-soluble liver antigen antibody, Primary biliary cholangitis, Autoimmune hepatitis

OP-042

Prevalence of Antimitochondrial Antibody and Primary Biliary Cholangitis in Korea: A Single Center Study

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Aims: Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis is classified as rare disease in South Korea. Anti mitochondrial antibody (AMA) is a signature antibody for PBC diagnosis. Ninety percent of PBC patients are AMA positive. The prevalence of AMA positivity in general population in South Korea is not well studied. We aimed to investigate the prevalence of AMA positivity in our hospital.

Methods: We retrospectively reviewed patients who were tested for AMA, from 2014 to 2018. All patients who had hepatitis B or C were excluded form analysis. Clinical data including age, sex, laboratory findings and image studies were also reviewed.

Results: Total of 1,120 pateints were tested for AMA during this period. Among 1,120 patients tested, 40 patients were AMA positive. Among 190 with Alkaline phosphatase level higher than upper limit of normal (ULN), 11 were AMA positive. Among 664 with γ-Glutamyl Transpeptidase level higher than ULN, 21 were AMA positive. Among 40 patients with AMA positive, 36 were female, mean age were 62 years old. Anti nuclear antibody was positive in 28 patients. Liver biopsy were performed in 19 patients. 14 were diagnosed as AIH-PBC overlap syndrome. 16 Patients had evidence of liver cirrhosis, and two have developed Hepatocellular carcinoma (HCC) during follow up.

Conclusions: Positive rate of AMA in our patients were higher than anticipated considering estimated prevalence of PBC in Korean population. Prognosis of PBC is good when treated early with UDCA. Considerably large number of PBC patients are presumed underdiagnosed. AMA should be actively tested when clinically suspected. Larger studies are needed to estimate true prevalence of AMA and PBC in Korea.

Keywords: Primary biliary cholangitis, Anti mitochondrial antibody, Prevalence, Korea

[Group 8] June 21, 2019 | 15:30-16:30

Liver Transplantation

OP-043

Liver Transplantation for Patients with Pre-Existing Portal Vein Thrombosis: A Single-Center Experience

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Aims: Portal vein thrombosis (PVT) is not uncommon in liver cirrhosis patients. In past, PVT had been considered as contraindication to liver transplantation (LT) because of technical challenges for adequate restoration of portal inflow followed by high morbidity and mortality. However, alternative options for PVT during LT have been introduced, and nowadays, PVT is no longer considered as absolute contraindication for LT. Herein, we introduce our experiences and outcomes of LT for patients with PVT.

Methods: Between Mar 2014 and June 2018, 65 patients underwent LT at out institution, and 13 (20%) of whom had PVT preoperatively. The characteristics and management of these patients were reviewed retrospectively and the outcomes were compared with that of non-PVT group.

Results: The type of PVT included Yerdel grade 1 in 7 patients (53.8%), grade 2 in 4 patients (30.8%), grade 3 in 1 patient (7.7%) and grade 4 in 1 patient (7.7%). For restoration of portal inflow, eversion thrombectomy was performed in 11 patients (84.6%), reno-portal bypass in 1 patient (7.7%) with grade 4 PVT, and SMV jump graft in 1 patient (7.7%) with grade 2 PVT. There was no portal vein-related morbidity except one patient who need portal vein stent because of stricture. The outcome after LT was comparable with that of patients without PVT.

Conclusions: Although it has a technical complexity in surgical procedure, LT is no longer contraindication for patient with PVT because of various alternative options and the outcome is comparable with the patient without PVT.

Keywords: Portal vein thrombosis, Liver transplantation, Reno-portal bypass, Jump graft

OP-044

Accuracy of Noninvasive Methods to Estimate Hepatic Steatosis in Living Liver Donors

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Aims: In living donor liver transplantation (LDLT), steatosis of the liver graft is very important for the safety of both donors and recipients. The purpose of this study was to evaluate the accuracy of noninvasive methods to estimate hepatic steatosis and find the most reliable one.

Methods: From January 2014 to September 2018, 214 patients were performed donor hemi-hepatectomy (right lobe) in our center. Patients were divided into 4 groups by the macro-vesicular steatosis based on the pathologic report (Group 1: <5%, Group 2: 5≤ and <10%, Group 3: 10≤ and <20%, Group 4: ≥20%). Hepatic and splenic attenuation values were measured on non-contrast CT scans by using circular region-of-interest (ROI) cursors in the liver and spleen. In MRI, steatosis was measured by MR spectroscopy.

Results: Of the 214 donors, 118 (55.1%) were in group 1, 61

(28.5%) were in group 2, 23 (10.8%) were in group 3, and 12 (5.6%) were in group 4. There were no statistical differences in age and sex among 4 groups. But, body mass index (BMI), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly different among 4 groups. Liver-to-spleen CT ROI values ratio (L/S ratio) on non-contrast CT was significantly correlated with graft steatosis with a correlation coefficient of 0.176 (P<0.001). MR spectroscopy also showed significant correlation with graft steatosis with a correlation coefficient of 0.289 (P<0.001).

Conclusions: Both L/S ratio and MR spectroscopy were able to estimate graft steatosis to some extent. And among them, MR spectroscopy was more relevant with histopathologic steatosis assessment.

OP-045

Neutrophil-to-Lymphocyte Ratio Predicts Acute Cellular Rejection in Living Donor Liver Transplantation

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Aims: The neutrophil-to-lymphocyte ratio (NLR) predicts poor prognosis in several conditions including transplantation. The aim of the study was to evaluate the effectiveness of NLR in prediction of ACR after living donor liver transplantation (LDLT).

Methods: This was a retrospective study of patients who underwent liver biopsy after LDLT from 2009 to 2017. The NLR was calculated 4 weeks before transplantation, at the time of transplantation, and immediately prior to liver biopsy. The correlations between NLR values and the incidence of ACR were investigated.

Results: Eighty-one patients were reviewed (ABO-compatible (ABOc) = 66, ABO-incompatible (ABOi) = 15)). ACR occurred in 19 (28.8%) ABOc LDLT. ACR occurred within 1 month after transplantation in 15 (78.9%) ABOc LDLT. There was no significant difference 4 weeks before transplantation (ACR: no-ACR = 2.54 ± 1.15 : 3.68 ± 2.08, P=0.06) and transplantation (ACR: no-ACR = 20.53 ± 13.39 : 17.73 ± 8.74, P=0.06). However, NLR immediately prior to biopsy was significantly lower in the ACR group (ACR:no-ACR = 5.82 ± 3.42 : 28.66 ± 22.66, P<0.001). Liver function tests (LFT) in the ACR and no-ACR groups in ABOc LDLT were not significantly different. For prediction of NLR for ACR within 1 month in ABOc, the ROC revealed an AUC of 0.969. The NLR cut-off of 9.67 had a sensitivity 94.1% and specificity 86.7%.

Conclusions: NLR could be a non-invasive predictor of subclinical early ACR in ABO-compatible LDLT.

OP-046

Hepatitis B Vaccination and Entecavir Monotherapy Following Withdrawal of Hepatitis B Immunoglobulin (HBIG). An Alternative Approach to Prevention of Hepatitis B Reactivation after Liver Transplantation

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Aims: Combination of HBIG with an oral nucleoside / nucleotide analog (Entecavir/Tenofovir) has been the mainstay of prevention of Hepatitis B reactivation after liver transplantation.. HBIG is costly, inconvenient, and may contribute to development of mutant strains. There are no consensus guidelines regarding the role of Hepatitis B vaccination in prevention of Hepatitis B reactivation after liver transplantation.

Methods: 41 liver transplant recipients on Entecavir alone were given Hepatitis B vaccination once antibody titres were undetectable. HBIG was withdrawn from all patients. The response to a standard 3 dose regimen of Hepatitis B Vaccine was evaluated. Reactivation of Hepatitis B was defined as HBsAg positive titre.

Results: Mean age was 60.54 (44-74). 27 were DDLT, 14 were LDLT. Mean BMI was 23.56 (16.27-32.47). Mean MELD score and CTP score was 15.73 and 8.56 respectively 33 patients were transplanted for Hepatitis B related HCC and 8 were for Hepatitis B related hepatic decompensation. No recurrence or adverse events occured. 34/36 (5 drop outs) patients had undetectable HBsAb titres. 9 patients had positive response to vaccination. 2 patients had persistent antibody titres (not vaccinated). 1 patient responded after a fourth dose. 2 patients had no response even after 4 doses and 1 no response after 6 doses. A significant positive response to vaccination was seen in patients receiving single immunosuppressive agent compared to a combination (P=0.048).

Conclusions: A standard 3 dose Hepatitis B Vaccination regime may confer additional immunity. Patients who are on single immunosuppressive agent are more likely to develop a positive response to vaccination.

OP-047

Living Liver Donor Surgical Complication: Single Center Experience with 512 Cases

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Aims: Korea is the one of the most common country to do living donor liver transplantation. We were reached to 500th living donor liver transplantation in 2017. We review our donor

complication and find way to reduce the rate of morbidity.
Methods: Institutional LT database was searched from 2005.05.08. to 2017.12.31. Their medical records and imaging studies were reviewed.
Results: From 2005.05.08 we did first living donor hepatectomy, we did 512 living donor hepatectomy until 2017.12.31. Among them, 324 were male and 188 were female. Graft types were Right liver graft in 457 (89.3%), Left liver graft in 47 (9.2%), Left lateral section graft in 2 (0.4%) and Right posterior section graft in 6 (1.2%). Mean age of total donor was 30 years and Mean BMI was 22. Mean hospital days was 10days. All of the donors, surgical complication occurred in 32donors (6.3%). Minor complication was 10 cases(1.9%). Major complication was 24 case (4.7%). Between major complication, the most common complication was biliary complication (n=17) and the Other complications were small bowel obstruction operation (2), bleeding control (n=2), pleural effusion drainage (n=2), portal vein stent insertion (n=1). There are no mortality. There are re-operation case was just one case, which was immediate right hepatic artery bleeding.
Conclusions: Our center's complication was very low. But still biliary complication is the most common complication. When we meet abnormal biliary anatomy we must be careful and we try to reduced biliary complication.

OP-048

Right Anterior Section Graft for Living-Donor Liver Transplantation

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Aims: In living-donor liver transplantation, the right lobe graft is commonly utilized to prevent small-for-size syndrome, despite the considerable donor morbidity. Conversely, the feasibility of the left lobe graft and the right posterior section graft in smaller-sized recipients is now commonly employed with comparable outcomes to right lobe grafts. The efficacy of the right anterior section graft has rarely been reported.
Methods: Here, we describe a 56-year-old man, with alcoholic liver cirrhosis, who successfully underwent living-donor liver transplantation using the right anterior section graft.
Results: Preoperatively, the right lobe of the donor occupied 76.2% of the total liver volume exposing the donor to a small residual liver volume. The right posterior section and left lobe volumes were insufficient, providing a graft-to-recipient weight ratio of 0.42% and 0.38%, respectively. However, the right anterior section could fulfill an acceptable GRWR of 0.83%. Clinical signs and symptoms and liver function improved following anterior section graft transplantation without complications.
Conclusions: The procurement of anterior section graft is technically feasible in selected patients, especially in high-volume liver centers.

OP-049

Propensity-Score Matching Analysis of Postoperative Outcome Including Quality of Life after Single Incision Versus Multiport Laparoscopic Cholecystectomy: A Nationwide Prospective Multicenter Study in Korea

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Aims: There is still controversy for usefulness of single incision laparoscopic cholecystectomy (SILC) compared to multiport laparoscopic cholecystectomy (MPLC) due to no clear indication and technical difficulties. SILC could reduce the number of ports, but cause more postoperative pain and worsen quality of life (QoL) because of large umbilical incision. The purpose of this study was to compare postoperative outcomes of SILS with those of MPLC.
Methods: In a prospective Korea Cholecystectomy Quality Improvement Program cohort including 18 institutions from October 2016 to March 2017, 2510 patients who underwent laparoscopic cholecystectomy for benign gallbladder disease were enrolled. Various postoperative outcomes were compared between two groups including operative details, postoperative complications, pain assessed by NRS score, and QoL assessed by GIQLI questionnaire after propensity score matching (PSM) with 1: 2 balances using multiple covariates, such as, age, sex, ASA classification, comorbidities, biliary drainage, and pathology of acute cholecystitis.
Results: Among study cohort, SILS were performed 331 patients, whereas MPLC were 2179 patients. After uni- and multivariate analysis, there were no significant differences in terms of operative finding including operative time (46±20 min. vs 45±24 min., *P*=NS) and difficulty, postoperative complications including biliary injury. Also, there were no significant differences in terms of postoperative pain (2.1±1.9 vs. 2.3±2.3, *P*=NS) and QoL (1.8±2.1 vs. 1.7±1.6, *P*=NS).

Conclusions: SILC showed comparable postoperative outcomes including operative findings, postoperative complications, and patients- reported outcomes after PSM analysis with a nationwide prospective data. In conclusion, SILC is as safe as MPLC for benign gallbladder disease compared with MPLC.

OP-050

Laparoscopic Total Pancreatectomy in Benign and Borderline Malignant Tumor of the Pancreas: Perioperative Outcomes and Quality of Life

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Aims: Laparoscopic pancreas surgery has been practiced with development of the surgical technique and the laparoscopic instrument. Also total pancreaticoduodenectomy has been applied for benign and borderline pancreatic disease.
Methods: From 2005 to 2018, 19 consecutive patients underwent laparoscopic total pancreatectomy (Lap TP) and 32 patients underwent open total pancreaticoduodenectomy (Open TP) in Yonsei University severance Hospital. Among them we were select the patient who diagnosed benign and borderline pancreatic tumor and renal cell carcinoma metastases to pancreas. The results showed 19 patients underwent laparoscopic total pancreatectomy and 10 patients underwent open total pancreatectomy. We compared the perioperative outcomes and quality of life (QoL) between Lap TP and Open TP. But, we did not conduct a questionnaire on patients who underwent total pancreatectomy for less than 1 year.
Results: The mean age of Lap. TP was 66.9±10.1 and the mena age of open TP was 52.0±13.9. And The mean BMI of Lap TP was 22.7±2.5 and Open was 28.9±12.8. the Operation time of Lap TP was 503.1±86.9 and open TP was 485.1±215.9. And the EBL of Lap TP was 488.9±191.1 and open TP was 1318.8±1140.5. The length of hospital in Lap TP was 15.1±4.5 and open TP was 23.5±12.5. The QoL betwee Lap TP and open TP was not statistically significant different.
Conclusions: Lapa TP is feasible and safe in case of benign and borderline pancreatic tumor, even if case with metastatic renal cell carcinoma. And Lap TP procedure could be applied to benign and borderline pancreatic tumor and metastatic RCC to pancreas.

OP-051

BMPR2 Promotes Pancreatic Cancer Proliferation via the GRB2-Mediated PI3K-Akt-mTOR Pathway

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Aims: Tumor microenvironment favors aberrant expression of tumor cells characterized by dysregulated release of cytokines, chemokines, and growth factors that the tumor exploits for survival and invasion. The crosstalk of bone morphogenetic proteins and its receptors between tumor and its surrounding stromal cells have been reported in breast cancer, but effects of the interaction in pancreatic cancer remain unclear.
Methods: The enrichment of BMP pathway gene set was anlaysis by GSEA software in three database of GEO. BMPR2 were reduced in PDAC cells via specific shRNA-mediated knockdown. Quantitative proteomic analysis was performed to explore the mechanism of BMPR2 regulation. The cell growth rate was assessed by CCK-8, FACS and colony formation assays. ChIP-sequence was performed to identify and characterize smad complexes target genes.
Results: Here we demonstrate that BMP pathway was hyperactived in pancreatic cancer.BMPR2 was overexpressed in human pancreatic cancer specimens and associated with the prognosis of pancreatic cancer patient. Down-regulated BMPR2 markedly inhibits the growth of pancreatic cancer cell lines Mia-PaCa-2 and PANC-1 in vitro and vivo. Mechanistically, disrupt the expression of BMPR2 suppresses the expression of GRB2 in a smad-independent manner, and then inactivates GRB2-associated signaling pathways, PI3K-Akt-mTOR pathway. In addition, LDN193189, a BMP pathway inhibitor, can also impair the expression of BMPR2 and inhibit the functions of pancreatic cancer cells by GRB2-mediated PI3K-Akt-mTOR pathway.
Conclusions: Thus, our results suggest that BMPR2 is an important mediator of pancreatic cancer cells and its surrounding microenvironment and offer insight into therapeutic applications for better survival of patients with this deadly disease.

OP-052

Pre-Drainage and Post-Drainage Prognostic Nomograms to Predict Outcome of Percutaneous Drainage in the "Step-Up Approach" for Necrotizing Pancreatitis

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Aims: Percutaneous catheter drainage (PCD) with saline irrigation alone is effective in a large proportion of patients with pancreatic necrosis treated with the step-up approach. Early identification of patients who are likely to fail PCD helps in early referral and treatment.
Methods: Single-center retrospective cohort study using data from a prospectively maintained database. Patients with necrotizing pancreatitis undergoing PCD as initial intervention were included. Patients who did not respond underwent necrosec-

tomy. Univariate and multivariate analysis for predictors of PCD failure (i.e. mortality or need for necrosectomy) were performed. Models were constructed for pre- and post-drainage use, and were internally validated.

Results: A total of 304 patients were included, of which 221 (72.6%) had severe disease. PCD was successful in 59.8%. Overall mortality was 26%. The pre-drainage model consisted of APACHE-II score at admission, early organ failure and pancreatic necrosis >50%. The post-drainage model consisted of APACHE-II at first PCD, early organ failure, pancreatic necrosis>50%, sepsis reversal within one week of PCD and E. coli in initial PCD culture. Both models were internally validated with bootstrapping with 3000 resamples and area under ROC curve was 71.2% for pre-PCD and 81.2% for the post-PCD model. Prognostic nomograms were constructed to determine the probability of PCD failure. On plotting calibration curve, both models showed high reliability.

Conclusions: Percutaneous catheter drainage with saline irrigation alone was successful in 59.8% with mortality of 26%. Both pre- and post-PCD models were well-calibrated and reliable. These nomograms can help in guiding treatment strategy and early referral of high-risk cases.

OP-053

Comparison of the Prognostic Impact and Combination of Preoperative Inflammation-Based and/or Nutritional Markers and 18F-FDG-PETCT-Derived Markers of Tumor Metabolism in Patients with Bile Duct and Pancreatic Cancer

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Aims: The aim of this study was to evaluate and compare the prognostic value of preoperative established inflammation-based and/or nutritional markers and 18F-FDG-PETCT-derived markers in patients with bile duct and pancreatic cancer.

Methods: This study retrospectively reviewed 80 patients who underwent R0 resection for bile duct and pancreatic cancer. C-reactive protein-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio, platelet to- lymphocyte ratio, Prognostic Nutritional Index (PNI), Glasgow Prognostic Score, were derived from routine blood tests. The maximum standardized uptake (SUVmax), peak standardized uptake (SUVpeak), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were measured.

Results: There was no association between 18F-FDG-PETCT measures of tumor metabolism and systemic inflammation. Among inflammation-based and/or nutritional markers and 18F-FDG-PETCT-derived markers, multivariate analyses demonstrated CAR, PNI, SUVmax, MTV and TLG as independent prognostic factors for OS, respectively.

Conclusions: The present study reports a direct association between 18F-FDG-PETCT-derived measures of tumor metabolism and systemic inflammation in patients with bile duct and pancreatic cancer.

OP-054

Risk of Atherosclerotic Cardiovascular Diseases in Patients with Pancreatitis: A Retrospective Cohort Study

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Aims: The association between atherosclerotic cardiovascular diseases (ASCVD) and pancreatitis remains incompletely understood. Our purpose is to evaluate the long-term risk of ASCVD in patients with pancreatitis.

Methods: A retrospective cohort study was performed to analyze the database of Taiwan's National Health Insurance. We identified the pancreatitis cohort included 2737 patients age 20 years or older with new-onset pancreatitis between 2000 and 2008. A comparison cohort of 10948 adults without pancreatitis was selected from the same dataset, with matching by age and sex. Both cohorts had no histories of ASCVD (included stroke and acute myocardial infarction) before the index date. Events of incident ASCVD in 2000-2013 were identified from medical claims during the follow-up period. Adjusted hazard ratios (HRs) and 95% CIs of incident ASCVD associated with pancreatitis were calculated.

Results: The incidences of ASCVD for pancreatitis cohort and comparison cohort were 13.1 and 7.1 per 1,000 person-years, respectively (P<0.0001). Compared with comparison cohort, the adjusted HR of incident ASCVD was 1.85 (95% CI 1.56-2.20) for people with pancreatitis. The association between ASCVD and pancreatitis was significant in various subgroups. History of alcohol-related illness (HR 5.65, 95% CI 4.01-7.95), liver cirrhosis (HR 4.45, 95% CI 3.11-6.36), diabetes (HR 2.68, 95% CI 2.11-3.40), and cholecystitis (HR 2.38, 95% CI 1.41-4.03) worsen the risk of ASCVD in patients with pancreatitis.

Conclusions: People who had pancreatitis may have increased risk of incident ASCVD compared with those without pancreatitis. Our findings warrant a survey and education on ASCVD for patients with pancreatitis.

Keywords: Atherosclerotic, Cardiovascular diseases, Pancreatitis, Stroke, Acute myocardial infarction

[Group 1] June 22, 2019 | 13:20-14:20

HBV

OP-055

The Significance of Early Virological Response in the Patients with Prolonged Antiviral Treatment for Chronic Hepatitis B

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Aims: Due to the potent oral antiviral agents for chronic hepatitis B (CHB), prolonged therapy could expect not only complete viral suppression but also HBsAg loss. Several reports issues whether the suboptimal response under oral antiviral therapy was associated with a higher risk of HCC. However, there remains uncertain about the impact of early virological response on serological response including HBeAg loss and HBsAg loss in the patients whose long-term therapy is inevitable.

Methods: A total of 4,011 consecutive patients who were treated with entecavir (n=1,956) or tenofovir (n=1,421) at three St. Mary's Hospital of Catholic University between 2007 and 2016 were investigated. Early virological response is defined as HBV DNA <20 IU/ml at week 48 of therapy. The response rates of HBeAg and HBsAg were analyzed depending on the early virological response.

Results: Median follow-up period was 55.9 months (6.2-99.8 months). The patients with HBeAg positive were 2,022 (50.4%) and early virological response was achieved in 1,394 patients (68.9%). During follow-up, cumulative rate of HBeAg loss was 40.1%. HBeAg loss was a higher rate in patients with early virological response than with partial virological response (45.5% vs. 28.3%, *P*<0.001). HBsAg loss was achieved in 17 of 2,022 patients (0.8%). Achievement of HBsAg loss was much favor in complete virologic response group than partial virologic response group (1.1% vs. 0.2%, *P*=0.023). In the patients with HBeAg negative, early virologic response was achieved in 89.9% (1,219 of 1,355 patients). In this group, culmulative rate of HBsAg loss was not different between the patients with early virologic response and with partial virologic response (1.1% vs. 1.5%, *P*=0.657).

Conclusions: Our results demonstrated that early full virological suppression is associated with a higher chance of HBeAg loss and finally HBsAg loss in HBeAg positive patients with prolonged antiviral therapy. However, its role is unclear in the HBeAg negative patients.

Keywords: Chronic hepatitis B, Virological response, HBeAg loss, HBsAg loss

OP-056

No Resistance to Tenofovir Alafenamide (TAF) Detected through 144 Weeks of Treatment in Patients with Chronic Hepatitis B (CHB)

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Aims: Cumulative resistance analyses were performed through Week 144 for 2 Phase 3 studies (GS-US-320-0108, GS-US-320-0110) evaluating TAF or tenofovir disoproxil fumarate (TDF) for the treatment of CHB in HBeAg+ and HBeAg- treatment-naïve or treatment-experienced adults.

Methods: Patients were randomized 2:1 to receive TAF or TDF double-blind (DB) treatment for 144 weeks, and were then switched to open-label (OL) TAF. HBV pol/RT deep sequencing was conducted for any patient with ≥24 weeks of treatment and HBV DNA ≥69IU/mL at Week 144 or at early discontinuation. Illumina Mi-Seq deep sequencing was conducted and sequence changes at the consensus sequence level (15%) were reported. In vitro phenotypic analysis using recombinant HBV in HepG2 cells was performed for: VB patients who were adherent to study drug, those with conserved site substitutions, or when polymorphic substitutions emerged in >1 patient.

Results: 1298 patients were randomized and treated with TAF (n=866) or TDF (n=432). Through Week 144, 9.9% (TAF, 10.4%; TDF DB, 11.9%) of enrolled patients qualified for sequencing at their last evaluable visit; Of these 128 patients, 63 had no sequence change from baseline, 22 were unable to sequence due to lower viral load, 31 had polymorphic site substitutions, and 12 had conserved site substitutions. Cumulatively, 70 patients qualified for phenotypic analysis and no isolates showed reduction in susceptibility to TAF or tenofovir (TAF: n=54, mean fold change EC50 0.99, range 0.32-1.68; tenofovir: n=16, mean fold change EC50 0.92, range 0.33-1.45).

Conclusions: No substitutions associated with resistance to TAF were detected through 144 weeks of treatment.

Keywords: TAF, Resistance, 144 weeks, CHB

OP-057

Low-Level Viremia and Cirrhotic Complications in Chronic Hepatitis B Patients with Good Adherence to Entecavir

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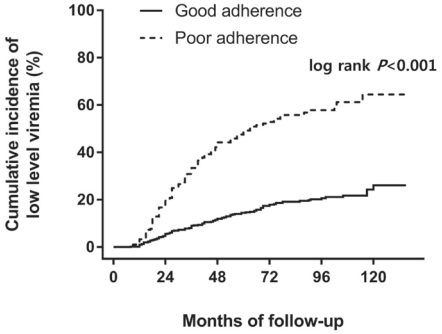
Aims: Low-level viremia (LLV; <2,000 IU/mL) to nucleos(t)ide analog treatment was presented as possible cause of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB). However, detailed information on adherence was lacking. This study aimed to evaluate the effect of LLV on HCC development, as well as on mortality and cirrhotic complications among patients with good adherence to entecavir (ETV) treatment in real-world clinical settings.

Methods: We performed a 10-year retrospective observational analysis of data from 894 consecutive adult patients with treatment-naïve CHB undergoing ETV treatment. LLV was defined by either persistent or intermittent episodes of <2,000 IU/mL detectable hepatitis B virus DNA during the follow-up period. Good adherence to medication was defined as a cumulative adherence ≥90% per study period.

Results: In the entire cohort (n=894) that did not consider adherence, cumulative incidence of HCC was significantly lower in the maintained virologic response (MVR) group than in the LLV group (log rank *P*=0.017). Multivariate analysis for the HCC incidence showed that LLV was an independent prognostic factor in addition to other traditional risk factors in the entire cohort. The good adherence group comprised 617 patients (69.0%). No significant difference was found between the MVR and LLV groups in terms of the incidence of liver-related death or transplantation, HCC, and hepatic decompensation in the good adherence group according to univariate and multivariate analyses.



Number at risk						
Good adherence	617	535	436	332	176	39
Poor adherence	277	199	108	68	35	5

Conclusions: In treatment-naïve CHB patients with good adherence to ETV treatment in real-world clinical settings, LLV during treatment was not a predictive factor for HCC and cirrhotic complications, even if cirrhosis.

Keywords: Adherence, Hepatitis B virus, Hepatocellular carcinoma, Low-level viremia

OP-058

Tenofovir Disoproxil Fumarate on the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients with Failure to Preceding Treatments

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Aims: Tenofovir disoproxil fumarate (TDF)-monotherapy is recommended for the treatment of chronic hepatitis B (CHB) patients who are refractory to other drugs. Yet, little data are available for the effectiveness of TDF-monotherapy compared with TDF-based combination therapy on the risk of hepatocellular carcinoma (HCC) and death/transplantation.

Methods: This historical cohort study included 1,163 CHB patients who initiated TDF rescue therapy after persistent viremia and genotypic resistance mutations from the failure of preceding treatments between January 2012 and December 2015 at Asan Medical Center in Korea. The risks of HCC and death/transplantation of TDF-monotherapy (n=848) groups were compared with those of TDF-based combotherapy (n=315) groups.

Results: During 5.1 years of overall follow-up period, 60 (5.2%) patients developed HCC, and 23 (2.0%) died or received liver transplantation. In the 295 propensity score-matched pairs, compared with TDF-combotherapy, TDF-monotherapy showed no significantly high risks of HCC (1.27/100 person-year [PY] vs. 1.10/100 PY; HR 0.87, 95% CI 0.46–1.64, *P*=0.66) and death/transplant (0.55/100 PY vs. 0.57/100 PY; HR 1.63, 95% CI 0.53–4.98, *P*=0.39). In the 101 propensity score-matched pairs of cirrhosis subcohort, TDF-monotherapy was associated with a similar risk of HCC and death/transplant compared with TDF-combotherapy (HR 1.29, 95% CI 0.62–2.67, *P*=0.50 and HR 1.03, 95% CI 0.21–5.15, *P*=0.97). The findings were consistently identified through inverse probability treatment weighting and competing risks analyses.

Conclusions: In CHB patients with failure to preceding treatments, TDF-monotherapy showed no higher risks of HCC and death/transplantation compared with TDF-combotherapy. These findings suggest that TDF monotherapy can be an effective rescue treatment option for CHB patients with failure to preceding treatments.

Keywords: Hepatitis B virus, Liver cancer, Nucleos(t)ide analogue, Resistance

OP-059

Development of a Mathematical Modeling of HBsAg Kinetics during Long-Term Antiviral Treatment: A Pilot Study

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Aims: The kinetics of serum hepatitis B surface antigen (HBsAg) levels during nucleos(t)ide analog (NA) treatment needs to be elucidated for the prediction of off-treatment durability of response in patients with chronic hepatitis B (CHB). The aim was to develop a novel method of mathematical modeling for HBsAg kinetics under long-term NA treatment.

Methods: In this pilot study, we reviewed viral decay patterns and HBsAg kinetics in 184 CHB patients from a tertiary hospital in Korea who were treated with entecavir or tenofovir as their initial NAs, without evidence of antiviral resistance. HBsAg and immune effectors were added as new compartments in the model equations for hepatitis B viral dynamics. Parameter estimation was performed using the non-linear least square minimization method and non-linear Kalman filter algorithm.

Results: Mean age was 52.1±10.9 years, and 112 patients (60.9%) were male. Patients received either entecavir (93, 50.5%) or tenofovir (91, 49.5%). Median follow-up duration was 72.5 months. At baseline, 112 patients (60.9%) were HBeAg-positive. Baseline liver stiffness by transient elastography was 6.9 kPa (median; interquartile range [IQR], 4.6-11.1), and alanine aminotransferase (ALT) was 81.0 IU/L (IQR, 39.3-161.8). Baseline HBV DNA and HBsAg titers were 6.26 Log_{10}IU/mL (IQR, 5.34-7.54) and 2420.50 IU/mL (IQR, 1083.25-5342.12), respectively. The model equations for viral and HBsAg dynamics during antiviral treatment were developed as follows, considering i) both cytolytic and non-cytolytic clearance of infected cells, and ii) cccDNA and integrated HBV DNA in the host genome as dual sources of HBsAg:

$dT_1/dt = S - d_{T1} * T_1 - (1 - \eta)\, b * V * T_1$

$dT_2/dt = \alpha * f * I * E - d_{T2} * T_2 - (1 - \eta)\, b * V * T_2 + m_2 * T_2$

$dI/dt = ((1 - \eta)\, b * V (T_1 + T_2) + m_1 * I - d_I * I - \alpha * I * E$

$dV/dt = (1 - \varepsilon)\, p * d_I * I - c * V$

$dE/dt = S_E + b_E * I * E / (I + k_E) - d_E * E$

$sAg = \gamma * T_2 / (T_2 + k_T) + \delta * I / (I + k_I)$

(NOTE. T, target cell; I, infected cells; V, virus; E, immune effectors; sAg, HBsAg; d, death rate; η, treatment efficacy of inhibiting de novo infection; b, de novo infection rate of T; f, calibration coefficient of α for T; m, mitotic production rate of I; α, E-induced clearance rate of I; ε, treatment efficacy of inhibiting viral production; p, viral production rate by I; c, clearance rate of free virions; S_E, production rate of E; b_E, maximum birth rate for E; k_E, Michaelis-Menten type coefficient for E)

Figure 1 and 2 demonstrate sample visualization of the HBsAg kinetics with fitted curves using the model equations.

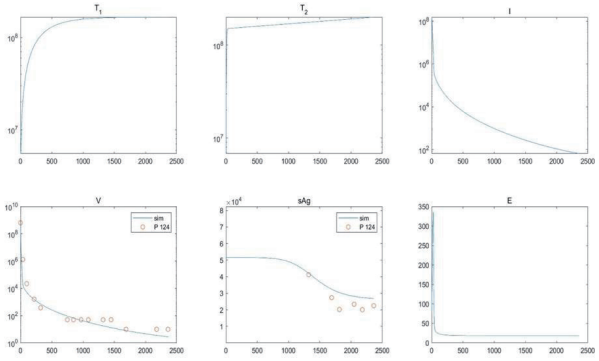

Figure 1.

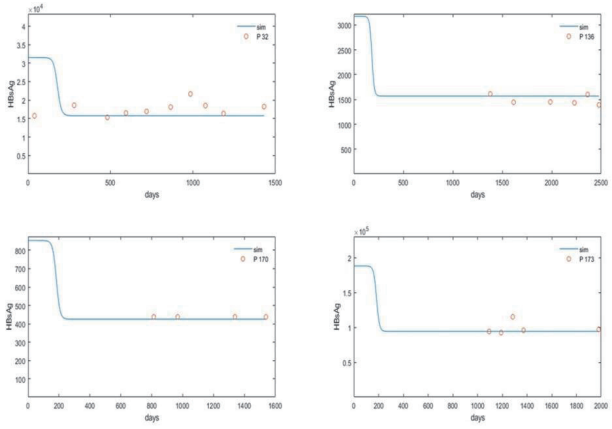

Figure 2.

Conclusions: Our novel mathematical model for hepatitis B viral dynamics showed promising results in terms of long-term fitting of HBsAg kinetics. These results need further validation in various clinical settings including discontinuation of NAs.

Keywords: Hepatitis B, Viral kinetics, HBsAg, Long-term treatment

OP-060

ALT Normalization after Entecavir and Tenofovir Correlated with Reduction of Development for HCC

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Aims: Recently, the use of potent antiviral agents has made it possible to effectively reduce liver disease related events such as hepatic encephalopathy, variceal bleeding, ascites, and HCC in patients with chronic hepatitis B. The aim of this study was to determine whether there is a relationship between normalized ALT resulting from the use of antiviral agents and the occurrence of liver disease related events.

Methods: From 2007 to 2018, we studied 427 patients treated

with entecavir or tenofovir at Korea University Guro Medical Center. The patients divided into ALT normal group and ALT abnormal group after 1 year of antiviral treatment. The ALT normal level is 34 for men, 30 for women in the KASL standard, and 35 for men and 25 for women in the AASLD standard. Liver related disease included HCC, hepatic encephalopathy, variceal bleeding, and ascites.

Results: The baseline characteristics of 427 patients median age was 50 (IQR 42~57), median value of AST was 78 (IQR 47~135 IU/L), ALT was 88 (IQR 45~178 IU/L), HBV DNA was 2,190,000 (IQR 170,000~36,815,316IU), and AFP was 7.05(IQR 3.325~26.025 ng/ml). 67% of all patients were male and 33% were female. 61.4% of patients used entecavir and 46.4% of patients used tenofovir. The people who used both drugs sequentially were 7.5%. Patients with HBeAg-positive were 54.8% and patients with anti-HBe Ab positive were 50.8%. Overall survival in ALT abnormal group was lower than ALT normal group after 1 year of antiviral treatment without statistical significance (Log rank test, P=0.201 in the KASL standard and P=0.265 in the AASLD standard). The cumulative incidence of HCC in normal ALT group was significantly lower than abnormal ALT group (Log rank test, P<0.001 in both the KASL and AASLD standard). The incidence of Liver disease related events in the two group was not significant (Log rank test, P=0.333 in the KASL and P=0.428 in AASLD standard).

Conclusions: ALT normalization after 1 year of entecavir and tenofovir treatment is correlated with reduction of development for HCC, but not overall survival and development of liver disease related events. Patients who failed to normalize ALT after 1 year of entecavir and tenofovir treatment should be observed more carefully for development of HCC.

Keywords: Chronic hepatitis B, ALT, Hepatocellular carcinoma

[Group 2] June 22, 2019 | 13:20-14:20

Cirrhosis & Liver Failure

OP-061

Effects of Atovastatin in Lowering Portal Hypertension in Patients with Cirrhosis

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Aims: Portal hypertension is most frequently associated with cirrhosis and is a major driver for associated complications: variceal bleeding, ascites and hepatic encephalopathy. Statins such as Atovastatin seem to be safe for patients with chronic liver diseases and exert multiple pleiotropic actions. Atovastatin improves liver generation of nitric oxide and hepatic endothelial dysfunction in patients with cirrhosis, so it could be an effective therapy for portal hypertension.

Aims: to assess portal hypertension using Doppler ultrasound in patients with cirrhosis before and after Atovastatin administration.

Methods: This study was conducted in Thai Nguyen National Hospital included 56 patients with cirrhosis and portal hypertension (hepatic venous pressure gradient- HVPG ≥ 12 mm Hg) who were dived into 2 groups: 28 patients with cirrhosis who were received 20 mg of Atovastatin daily for 2 weeks and then 40 mg daily for another 2 weeks, and control group included 28 patients with cirrhosis who did not receive Atovastatin. All patients underwent full clinical examination, laboratory investigations, and abdominal Doppler ultrasound at baseline and after 30 days to evaluate portal vein diameter (PVD), portal vein velocity (PVV), portal hypertension index (PHI), HVPG.

Results: PHI decreased significantly in group after Atovastatin administration for 30 days (a decrease of 8.1% from baseline, P<0.05). HVPG significantly decreases were observed in patients who were received Atovastatin (a decrease of 8.5% from baseline, P<0.05) and in those who were not (a decrease of 4.8% from baseline, P<0.05). No significant adverse effects were detected.

Conclusions: Atovastatin is safe and effective in lowering portal hypertension. Atovastatin decreased HVPG and improved liver perfusion in patients with cirrhosis. The beneficial effects of Atovastatin should be confirmed in many clinical trials for portal hypertension.

Keywords: Portal Hypertension, Atovastatin, Cirrhosis, Effects

OP-062

Low-Dose Propranolol as a Secondary Prophylaxis for Varix Bleeding Decreases Mortality and Rebleeding Rate in Patients with Tense Ascites

Jin Hwa Park, Dae Won Jun, Dae Hyun Lim, Won Woo Seo, Ji Hyun Yeo, Na Ryung Choi, Jai Hoon Yoon, Kang Nyeong Lee, Hang Lak Lee, Oh Young Lee, Byung Chul Yoon, and Ho Soon Choi

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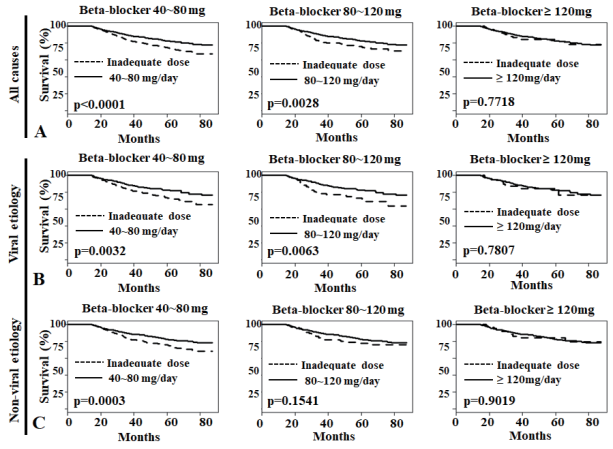
Aims: The risk and benefit of non-selective propranolol in patients with tense ascites are controversial. This study aimed to investigate the effect of propranolol as a secondary prophylaxis on variceal re-bleeding and overall mortality in patients with tense ascites.

Methods: This study used a database of the Health Insurance Review and Assessment Service (HIRAS), which provides health insurance to 97.2% of the total population in Korea. A total of 80,071 patients first variceal bleeding as the first decompensated complication enrolled from 2007 to 2014.

Results: There were 2,274 patients with large-volume ascites prescribed propranolol as a secondary prophylaxis after first variceal bleeding. The average prescription dose of propranolol as a secondary prophylaxis was 74 mg/day in patients with large-volume ascites. The mean duration of rebleeding was 22.8 months. Result of analysis showed that low-dose propranolol (40-120 mg/day) compared to inadequate propranolol dose (<40 mg/day) as a secondary prophylaxis decreased overall

mortality and varix rebleeding in patients with tense ascites.



Conclusions: Low-dose propranolol (40-120 mg/day) as a secondary prophylaxis for variceal re-bleeding decreased overall mortality and varix rebleeding recurrence in patients with tense ascites.

Keywords: Propranolol, Ascites, Mortality

OP-063

Endoscopic Variceal Obturation versus Retrograde Transvenous Obliteration for Fundal Variceal Bleeding

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Aims: Although both endoscopic variceal obturation (EVO) and retrograde transvenous obliteration (RTO) are recognized as effective in treatment of fundal varices in patients with liver cirrhosis, the studies comparing the therapeutic effect of EVO and RTO are very limited.

Methods: Patients with fundal variceal bleeding were enrolled, and patients with previous treatment of fundal varices were excluded.

Results: One-hundred twenty-three patients with fundal variceal bleeding were included. Age was 61.4±12.2 years and 88 patients (71.5%) were men. Alcoholic liver disease was most frequent underlying liver disease (63 patients, 51.2%). Type of varices was GOV2 and IGV1 in 60 (48.8%) and 63 (51.2%) patients, respectively. Eighty-seven patients (70.7%) and 36 patients (29.3%) were treated with EVO and RTO, respectively. There was a trend of higher MELD score in the EVO group than in the RTO group (13.2±4.3 vs. 11.6±4.0, *P*=0.061), while other baseline characteristics were comparable between two groups. During the follow-up period, GV rebleeding occurred in 16 patients (14 in the EVO group and 2 in the RTO group). GV rebleeding rates at 3, 6, 9, and 12 months after treatment were 2.9%, 5.2%, 7.6%, and 8.9%, respectively. GV rebleeding rates differed significantly according to the type of varices (*P*=0.022), while, GV rebleeding rates did not differ between EVO and RTO groups (*P*=0.107). On multivariate analysis, only type of varices was independent predictor for GV rebleeding (HR, 3.291; 95% Confidence interval, 1.059-10.227; *P*=0.040). During follow-up period, 19 patients died. Mortality did not differ according to the type of varices and type of treatment. On multivariate analysis, the MELD score was the independent predictor for mortality.

Conclusions: Both EVO and RTO are effective for preventing GV rebleeding in patients with fundal variceal bleeding. Type of varices was independent predictor for GV rebleeding in these patients.

Keywords: Endoscopic variceal obturation, Retrograde transvenous obliteration, Fundal varices, Bleeding

OP-064

Effect of Acute Kidney Injury on Long-Term Outcomes of Spontaneous Bacterial Peritonitis in Cirrhotics Using ICA-AKI Criteria

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Aims: Spontaneous bacterial peritonitis (SBP), a crucial complication of liver cirrhosis, is associated with high mortality. Acute kidney injury (AKI) is an important risk factor for the prognosis in cirrhosis. Recently, a new AKI criteria (International Club of Ascites, ICA-AKI) has been introduced in patients with cirrhosis. This study aimed to investigate the effect of AKI on long-term mortality of SBP in cirrhosis using ICA-AKI criteria.

Methods: A total of 157 cirrhotic patients with a first episode of SBP between January 2007 and December 2016 from three medical centers in Korea were analyzed. We investigated the long-term mortality with related risk factors of SBP in cirrhosis including the ICA-AKI criteria. The ICA-AKI stage at SBP diagnosis is as follows: stage 0, no increase of serum creatinine (SCr) or increase of SCr <0.3 mg/dl; stage 1, increase of SCr ≥0.3 mg/dl or SCr ≥1.5 - 2 times from baseline; stage 2, increase of SCr ≥2 - 3 times from baseline; stage 3, increase of SCr ≥3 times from baseline, or SCr ≥4.0 mg/dl with an acute increase of ≥0.3 mg/dl, or initiation of renal replacement therapy. Stage progression was defined as a progression of AKI to a higher stage.

Results: The mean age was 58.6 years. The etiology of liver cirrhosis was alcohol (n=73), hepatitis B virus (n=70), hepatitis C virus (n=9), and others (n=5). At the diagnosis of SBP, 106 patients were Child-Pugh class C (67%), the mean level of MELD score was 20.6, and the mean SCr level was 1.7 mg/dl. The ICA-AKI stage was stage 0 in 91 (58%), stage 1 in 33 (21%), stage 2 in 19 (12%), and stage 3 in 14 patients (9%). Stage

progression within 48 hours after SBP diagnosis was noted in 18 patients (12%). Of 157 patients, a total of 71 patients died (45.2%). The median time of overall survival was 6.7 months. Overall survival rates at 6, 12, 36, and 60 months were 50.2%, 45.2%, 43.7%, and 39.8%, respectively. Multivariable analysis showed that the risk factors for overall survival were Age ≥60 years (hazard ratio (HR) 1.74, *P*=0.029), serum sodium level ≤130 mmol/L (HR 1.3, *P*=0.017), ICA-AKI stage 1 (HR 2.51, *P*=0.003), ICA-AKI stage 2 or 3 (HR 3.36, *P*<0.001), and stage progression at 48 hours after SBP diagnosis (HR 2.57, *P*=0.004).
Conclusions: AKI and its progression are significant risk factors for mortality in cirrhotic patients with SBP. The new ICA-AKI criteria may be a useful tool to evaluate the prognosis of cirrhotic patients with SBP.
Keywords: Liver cirrhosis, Acute kidney injury, Albumin

OP-065

Severity Changes of Cirrhotic Patients during Seven Years Period in South Korea: A Multicenter Retrospective Study from 2008 to 2014

Jeong Han Kim, Eileen L.Yoon[1], Chung Hwan Jun[2], Jae Hyun Yoon[2], Byung Seok Kim[3], Jeong Eun Song[3], Ki Tae Suk[4], Moon Young Kim[5], Seong Hee Kang[5]

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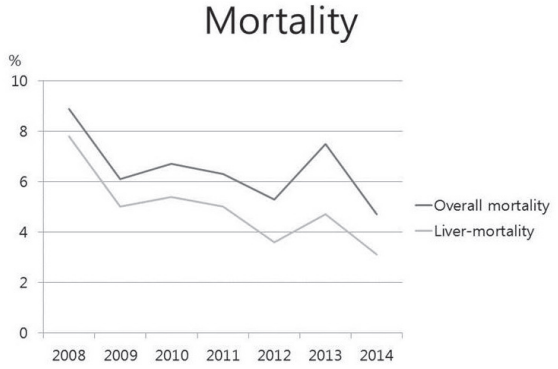
Aims: Clinical implications including disease severity of cirrhotic patients have been changed since oral antiviral agents for hepatitis B were introduced. On the other hands, alcoholic cirrhosis is still not well controlled and direct acting antiviral agents for hepatitis C are recently introduced. Therefore, we can expect improvement of severity will be observed more prominently in hepatitis B endemic area such as Korea. We aimed to investigate change of clinical severity in cirrhotic patients of Korea.
Methods: Medical records of 6,369 cirrhotic patients visited six tertiary university hospital in Korea from 2008 to 2014 were retrospectively reviewed. Clinical status of cirrhotic patients in each year was analyzed according to etiology, Child-Pugh score, decompensation, MELD score and mortality.
Results: Total 9,852 visit records were reviewed. Most common etiologies were hepatitis B and alcohol (38.6% and 39.7% each in 2008, and 35.1% and 39.0% each in 2014). Prevalence of decompensated cirrhosis did not decrease significantly from 45.2% in 2008 to 41.2% in 2014. Admission rate decreased from 56.8% in 2008 to 42.5% in 2014. Mean Child-Pugh score did not changed significantly from 6.6 to 6.4, but mean MELD score slightly reduced from 11.8 in 2008 to 10.9 in 2014. Overall mortality decreased from 8.9% in 2008 to 4.7% in 2014 and liver-related mortality also decreased from 7.8% to 3.1%. Among complications, variceal bleeding incidence reduced most significantly from 12.3% in 2008 to 7.8% in 2014. However, hepatocellular carcinoma (HCC) development rate did not decreased (9.8% in 2008 and 8.2% in 2014).



Conclusions: Alcohol became the most important etiology of liver cirrhosis in Korea, and overall clinical status was gradually improved. We can expect more improvement if treatment of hepatitis C and alcohol abstinence are successfully introduced. On the other hand, HCC surveillance is still important.
Keywords: Liver cirrhosis, Mortality, Decompensation, Hepatocellular carcinoma

OP-066

Clinical Features and Prognosis of the Patients with Chronic Liver Disease Hospitalized with Variceal Bleeding

Jung Hwan Yu[1], Young-Joo Jin[1], Jongbeom Shin[1], Jin-Woo Lee[1], Young Kul Jung[2], Hyung Joon Yim[2], Jin Mo Yang[3], Do Seon Song[3], Young Seok Kim[4], Sang Gyune Kim[4], Dong Joon Kim[5], Ki Tae Suk[5], Eileen Yoon[6], Sang Soo Lee[7], Chang Wook Kim[8], Hee Yeon Kim[8], Jae Young Jang[9], On Behalf of the Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

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Aims: Variceal bleeding is a critical acute deterioration causes in

the patient with cirrhosis. The aim of our study is to investigate the risk factor associated with mortality in the patients hospitalized with variceal bleeding and to evaluate the prognosis according to the presence of acute-on-chronic liver failure (ACLF).

Methods: This was a retrospective study conducted in patients from the Korean acute-on-chronic liver failure (KACLiF) study cohort, including 474 consecutive patients who were hospitalized with variceal bleeding from January 2013 to December 2013 in 21 hospitals. ACLF was defined by EASL-CLIF consortium (CLIF-C).

Results: Among a total of 474 patients, 61 patients were diagnosed with ACLF according to the CLIF-C. The cumulative overall survival rates (OS) of the patients with varix bleeding at 30 and 90 days became significantly lower, according to the ACLF grade (p-value<0.001). The combination of virus and alcohol, as a cause of underlying liver disease, represented poor prognosis of the patients with varix bleeding than other causes. In multivariate variable analysis, the significant predictive factor of OS of the patients hospitalized with varix bleeding was white blood cell (Hazard ratio, HR 1.01, P=0.029), c-reactive protein (HR 1.09, P=0.013), and CLIF sequential organ failure assessment (SOFA) score (HR 1.49, P<0.001). The CLIF SOFA score also was a significant predictive factor of OS in patients with ACLF and varix bleeding (P-value<0.001). CLIF SOFA score showed the reliable area under the receiver operating characteristic curve (AUROC) for the prediction of mortality at 30 (0.895, CI 0.829-0.962) and 90 days (0.896, CI 0.842-0.951).

Conclusions: In patients hospitalized with variceal bleeding, the presence of ACLF showed a poor prognosis, according to CLIF-SOFA score. Furthermore, CLIF-SOFA model represented reliable score for mortality prediction in patients with variceal bleeding.

Keywords: Chronic liver disease, Variceal bleeding

[Group 3] June 22, 2019 | 13:20-14:10

NAFLD

OP-067

Nonalcoholic Fatty Liver Disease and the Incidence of Myocardial Infarction: A Cohort Study

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[*]Contributed equally to this study; [†]Correspondence

Aims: Nonalcoholic fatty liver disease (NAFLD) is a multisystem disease associated with an increased risk of cardiovascular disease (CVD), diabetes, and chronic kidney disease. Indeed, CVD is the most common cause of death in NAFLD patients. In our study, we assessed whether the presence and severity of NAFLD was associated with the future development of myocardial infarction in a large cohort of asymptomatic adults without previous history of CVD.

Methods: A total of 111,492 adult men and women 40 years with no history of cardiovascular disease, liver disease or cancer at baseline who participated in a regular health screening exam between 2003 and 2013 were analyzed for incident myocardial infarction during follow-up. The main exposure was the presence of NAFLD at baseline. Fatty liver was diagnosed by ultrasonography, and NAFLD severity was assessed by the NAFLD fibrosis score (NFS).

Results: During 725,706.9 person-years of follow-up, 183 participants developed myocardial infarction (incidence rate 0.3 cases per 1,000 person-years). The age, sex, and year of visit-adjusted hazard ratio (HR) for incident myocardial infarction comparing participants with NAFLD to those without it was 2.14 (95% CI 1.59, 2.89). This association remained significant in fully-adjusted models (HR 1.54; 95% CI 1.11, 2.14). Compared to participants without NAFLD, the fully-adjusted HR for incident myocardial infarction in participants with low NFS (< -1.455) and with intermediate to high NFS (≥ -1.455) were 1.70 (1.22, 2.36) and 1.86 (1.22, 2.84), respectively.

Conclusions: In this large cohort study, NAFLD was associated with an increased incidence of myocardial infarction independently of established risk factors. In addition, this association was similar in participants with and without evidence of more advanced NAFLD as indicated by the NFS score. NAFLD patients may need to be carefully monitored and managed early to prevent myocardial infarction.

OP-068

Association between Body Size-Metabolic Phenotype and Nonalcoholic Steatohepatitis and Significant Fibrosis

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Aims: Body size-metabolic phenotype may help predict whether or not individuals with nonalcoholic fatty liver disease (NAFLD) develop advanced liver disease. We studied the association of body size-metabolic phenotype with nonalcoholic steatohepatitis (NASH) and significant fibrosis.

Methods: Our cross-sectional study included 559 subjects (mean age of 53 years; women 51%) with biopsy-proven NAFLD. Clinical, genetic, and histological characteristic features of NAFLD were evaluated. The metabolically unhealthy phenotype was defined by the presence of two or more metabolic components, while body size was categorized based on body mass index: obese (≥ 25 kg/m^2) or non-obese (< 25 kg/m^2). Body size-metabolic phenotypes were divided into four study groups: (1) metabolically-healthy/non-obese (MHNO), (2) metabolically unhealthy/non-obese (MUNO), (3) metabolically-healthy/obese (MHO), and (4) metabolically unhealthy/obese (MUO).

Results: MHO and MUNO groups demonstrated comparable levels of insulin resistance, adipose tissue insulin resistance indexes, and visceral adipose tissue (VAT) areas. The VAT area was significantly higher in the MUO group versus MHO group. However, the VAT to subcutaneous adipose tissue (SAT) ratio was highest in the MUNO group. There was no difference in histology between the MUNO, MHO, and MUO groups. Multivariate analyses adjusted for age, sex, smoking status, *PNPLA3*, *TM6SF2*, and VAT/SAT areas demonstrated an independent and dose dependent relationship between the body size-metabolic phenotype and NASH or significant fibrosis.

Conclusions: The MUNO group displayed similar degree of hepatic histological severity compared to their MHO counterparts. Metabolic milieu beyond obesity may play a pathogenic role in MUNO individuals who develop NASH with significant hepatic fibrosis.

Keywords: Hepatic steatosis, Non-obese, Body mass index, Metabolic syndrome

OP-069

Development of Machine Learning Model to Predict the 7-Year Risk of the Non-Alcoholic Fatty Liver Disease (NAFLD) among General Korean Population: A Nationwide Population-Based Study

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Aims: Even though early diagnosis and prognosis of NAFLD have become a necessity in clinical setting, there is no reliable methods to risk stratify for the risk of NAFLD.The aim of this study was to develop and validate a machine learning (ML) model to predict the 7-year risk of the risk of newly developed NAFLD among Korean general population using life style factors and anthropometric characteristics at baseline.

Methods: We used the data from the Korean health examinee (HEXA) study (baseline: 2004-2013, follow up: 2012-2017), which consists of the data on the life style factors (diet pattern, exercise, alcohol, smoking, stress index), and anthropometric indices (body mass index, waist circumference, fat mass, and muscle mass). After exclusion of the excessive alcohol ingestion, total of 40,745 participants who were free of NAFLD at baseline were finally enrolled and divided into test sets and training sets. ML algorithms includes support vector machine, random forest, artificial neural network, XGBoost, and ensemble methods. Area under receive operating curves (AUROC) of each methods were compared.

Results: During follow up period, incidental 5,232 cases of NAFLD cases were developed. ML model of Ensemble method for prediction of 7-year risk of NAFLD yielded AUCs of 0.85 (95% CI (95% CI 0.80 to 0.90) using lifestyle factors and anthropometric indices. XGBoosts model showed AUROC of 0.82 (95% CI 0.80 to 0.85).

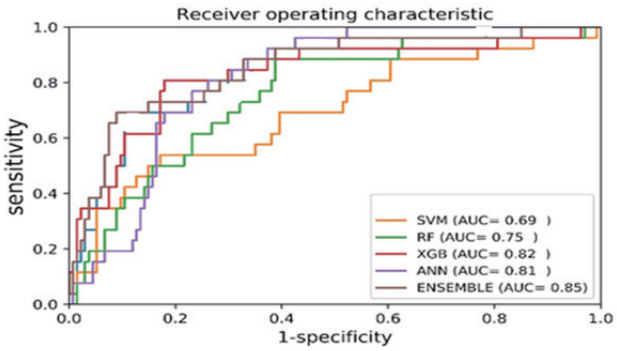

Figure 1. AUROC curves of ML(machine learning) based prediction model for the risk of NAFLD (non-alcoholic liver disease).
RF, random forest; SVM, support vector machine; ANN, artificial neural network, XGB, XGBoost; AUROC, area under curve receive operating curve.

Conclusions: ML based prediction model can be used to risk stratify 7-year risk of NAFLD among general Korean population, enable physicians to close follow up based on patients level estimation through ML algorithm.

Keywords: Machine-learning, NAFLD, Life style, Anthropometric

OP-070

Prevalence and Incidence of Tamoxifen-Related Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

Cheon Beom Lee[1], Jeong-Ju Yoo[1*], Sang Gyune Kim[1], Young Seok Kim[1], Soung Won Jeong[2], Jae Young Jang[2], Sae Hwan Lee[3], Hong Soo Kim[3], Baek Gyu Jun[4], Young Don Kim[4], Gab Jin Cheon[4]

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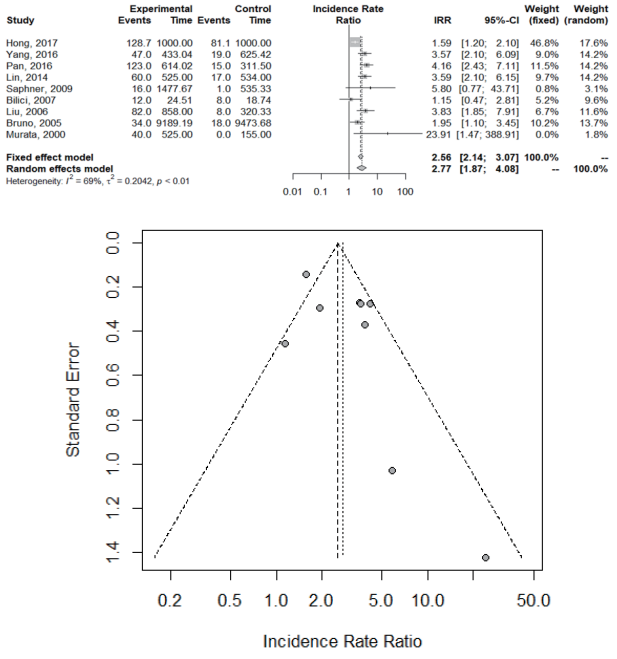
chunhyang University School of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Soonchunhyang University School of Medicine, Cheonan, Korea; [4]Department of Internal Medicine, Gangneung Asan Hospital, Gangneung, Korea

Background: It is well known that tamoxifen treatment is associated with an increased risk of developing nonalcoholic fatty liver disease (NAFLD). We conducted a systematic review and meta-analysis to evaluate the incidence of NAFLD using tamoxifen in breast cancer patients.

Methods: We searched PubMed, EMBASE, and the Cochrane Library from database inception to December, 2018, for studies reporting incidence of NAFLD using tamoxifen. Cross-sectional, cohort and randomized controlled trials with >25 participants were included. The lists of authors and abstracts from the search were reviewed by two investigators to determine the manuscripts for full text review. Event rates were calculated using a random-effects model.

Results: Twenty studies including 9796 patients met our inclusion criteria. The overall prevalence of obesity of tamoxifen induced NAFLD was 40.9% from 11 cross-sectional studies. The overall incidence of NAFLD was 71.0/1000 patient per years in tamoxifen group and 23.7/1000 patient per years in non-tamoxifen group from 1 randomized control trial and 8 cohort studies. The risk of NAFLD was much higher in tamoxifen group (incidence rate ratio 2.77, 95% CI 1.87-4.08, I^2=69%).



Conclusion: Use of tamoxifen is associated with increased risk of incidence and prevalence of NAFLD. Therefore, long-term use of tamoxifen requires clinical attention and regular liver imaging follow-up is required.

Keywords: Tamoxifen, Nonalcoholic fatty liver disease, Incidence, Prevalence

OP-071

Exosomal miRNA Analysis for Classifying Severity of Disease in Biopsy-Proven NAFLD Patients

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Aims: Nonalcoholic fatty liver disease (NAFLD) is becoming leading cause of chronic liver disease. Although determining the exact mechanisms that lead to NAFLD and NASH is important for disease identification, factors that regulate disease progression are largely unknown. In this study, we analyzed serum exosomal miRNA from biopsy-proven NAFLD patients and compared miRNA expression according to disease severity.

Methods: Sera were collected from 5 healthy volunteers and 21 patients with biopsy-proven NAFLD without other chronic liver disease from November 2016 to January 2018. Sera were stored at -20℃ and thawed for isolation of the exosomes. Exosomes were isolated from sera using an exosome isolation kit. Total RNA was extracted from exosomes and microarray analysis for miRNA was performed.

Results: Mean age and BMI were 53.5 ± 12.3 years and 29.9 ± 4.6 kg/m^2, respectively. Female was dominant (n= 17, 80.1%). In microarray analysis, total 2,578 miRNAs were identified. When we compared miRNA expression between healthy controls (n=5) and NAFLD patients (n=21), 21 miRNAs significantly increased in NAFLD patients comparing with controls and 34 miRNAs significantly increased in controls. (Figure) When patients were classified into NASH group (n=9) and non-NASH group (n=12), 5 miRNAs showed higher expression comparing with NAFL group including miRNA 122 and 185, whereas 3 miRNAs showed lower expression in NASH group comparing with NAFL group. Next, we classified patients into non-significant fibrosis group (F0-2, n=12) and significant fibrosis group (F3-4, n=9). 40 miRNAs expression increased in advanced fibrosis group comparing with non-advanced fibrosis group.

Conclusions: Exosomal miRNA expression analysis showed significant differences according to status of NAFLD, NASH, and fibrosis. These results mean exosomal miRNA expression might be important factor for disease progression in NALFD patients. Further validation studies are needed to identify the role of exosomal miRNA in disease progression of NAFLD.

Keywords: MiRNA, Exosome, NAFLD

[Group 4] June 22, 2019 | 13:20-14:20

Liver Cancer,Basic

OP-072

Updated Study on Action Mechanisms of Cereblon as a Novel Prognostic Biomarker for Hepatocellular Carcinoma

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Aims: Cereblon (CRBN) is a 50 kDa cytosolic protein that is known as an important player in various cellular functions in multiple myeloma, but little is known about the biological significance of CRBN in hepatocellular carcinoma (HCC). We presented the discovery process of CRBN as a new prognostic biomarker of HCC and developed prognostic prediction models of HCC using CRBN.

Methods: Laboratory study was focused on assessment of CRBN expression status and its regulatory mechanisms in vitro and in vivo studies. Post-resection prognosis of 212 patients with HCC of 2–5 cm was assessed according to CRBN expression.

Results: CRBN was highly expressed in HCC cell lines and patient-derived HCC samples, and very highly expressed in metastatic HCC. CRBN depletion decreased HCC cell motility and induced down-regulation of MMP-9 and MMP-2, whereas overexpression of CRBN increased migratory ability of HCC cells and expression of MMP-9 and MMP-2. In vivo CRBN depletion in patient-derived xenograft mouse models resulted in inhibition of tumor growth and suppression of EGFR and AKT/SOX2 pathways. Clinical study revealed that high CRBN expression showed higher tumor recurrence rate (P=0.027) and lower patient survival rate (P=0.015) than low CRBN expression. The prognostic impact of CRBN on HCC recurrence was greater than that of microvascular invasion (hazard ratio 1.97 vs. 1.46). Prognostic prediction models combining CRBN and other risk factors enhanced the prognostic prediction power (Harrel's concordance index >0.63).

Conclusions: CRBN is associated with aggressive tumor biology and has a high prognostic impact in HCC. Tumor aggressiveness was artificially changed according to the expression status of CRBN in vivo mouse model, which is the world-first finding in the field of HCC biomarker so far. We believe that CRBN is a new reliable prognostic biomarker of HCC.

Keywords: Biomarker, Cereblon, Prognosis, Prediction

OP-073

HKR3 Regulates Cell Cycle through the Inhibition of hTERT in Hepatocellular Carcinoma Cells

Sung Hoon Choi[1], Sung Ho Yun[2], Bora Jin[1,3], Kyung Joo Cho[1,3], Ha Young Lee[2,4], Simon W Ro[1,5], Do Young Kim[1,5], Sang Hoon Ahn[1,3,5], Kwang-hyub Han[1,3,5], Jun Yong Park[1,5]

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Aims: Hepatocellular carcinoma (HCC) is a malignant disease with improved hepatic regeneration and survival, and is activated by human telomere transferase (hTERT). hTERT is expressed during early fetal development and switched off in most adult tissues, but it becomes reactivated in HCC. The exact mechanism regulating these expression changes remains unknown during HCC progress. We evaluated the relationship between hTERT expression and human kruppel-related 3 (HKR3) and cell cycle-related factors in HCC cell lines.

Methods: Following transfection for hTERT knockdown and HKR3 overexpression, proteomic and transcriptomic analyses related to hTERT were performed using liquid chromatography/mass spectrometry (LC/MS) and RNA sequencing (RNAseq) in HCC cell lines. The expression levels of hTERT, HKR3, and cell cycle-related factors were measured using western blotting, and tumor growth were evaluated via cell proliferation and cell cycle assays.

Results: Transcriptomic and proteomic analyses showed that HKR3, hTERT and cyclin-dependent kinase inhibitor 2A (CDKN2A) were correlated. Up-regulation of HKR3 expression decreased hTERT and cyclin activation and increased CDKN2A activation. hTERT knockdown or HKR3 overexpression suppressed the G1/S phase of the cell cycle through CDKN2A activation.

Conclusions: Our results suggest that HKR3 is negatively correlated with telomerase activity. Increased CDKN2A through the inhibition of hTERT suppresses cell cycle regulation. Our results will facilitate further exploration of the pathways regulating human telomerase activity in HCC cell lines.

Keywords: HKR3, TERT, Proteomic, Cell cycle

OP-074

Circulating Exosomal microRNA-125b Inhibits Metastasis in Hepatocellular Carcinoma

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Aims: Exosomes are 30-100 nm-sized vesicles that are released from many cell types into the body fluids. Exosomal miRNAs have recently emerged as potentially promising biomarkers in

cancers and play an important role in cell to cell communication. The aim of this study is to investigate exosomal miRNAs contributing to extrahepatic metastasis from hepatocellular carcinoma (HCC).

Methods: Microarray-based miRNA profiling was performed to explore potential markers on the whole blood samples from patients with various liver diseases. Exosomes were extracted using exoquick and five miRNAs tested in sera of 47 healthy controls and 241 patients with and without metastasis. Then, target gene prediction was performed using TargetScan. Targets by miRNAs and epithelial-mesenchymal transition (EMT)-related protein expressions were assessed by Western blot. Biological functions of selected exosomal miRNAs in metastasis were investigated with a series of in vitro experiments including cell migration assay.

Results: Microarray-based miRNA profiling revealed 10 miRNAs with differential expressions, of which five exosomal miRNAs were further evaluated regarding metastasis. Transmission electron microscope and immunoblotting for exosomal markers confirmed the isolation of circulating exosomes from the patients. Among the selected miRNAs, exosomal miR-125b correlated with patient outcome, with increasing expression trends with tumor stage progression but followed by a significant drop with extrahepatic metastasis. Low exosomal miR-125b expression was associated with poor survival in patients as well as early metastases. For patients with serial serum samples before and after metastasis, exosomal miR-125b levels decreased upon metastasis. Transfection of HCC cells with miR-125b mimics downregulated SMAD2 and MMP2 known to regulate cancer metastasis. Moreover, miR-125b mimics inhibited migration ability of HCC cells.

Conclusions: Exosomal miR-125b has an anti-metastatic role by inhibiting cell migration and regulating EMT in HCC. Our findings suggest that exosomal miR-125b could be a potential biomarker and novel therapeutic target for metastasis from HCC.

Keywords: Exosome, Biomarker, Hepatocellular carcinoma, Metastasis

OP-075

Gut Microbes May Enhance the Efficacy of Immunotherapy in the Murine Metastatic Liver Cancer Model

Hyunwoo Oh[1], Minseok Albert Kim[1], Su Jong Yu[1,2], Hyojin Noh[2], Heejoon Jang[1], Sun Woong Kim[1], Cheol-Hyung Lee[1], Yun Bin Lee[1,2], Eun Ju Cho[1,2], Jeong-Hoon Lee[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1]

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Background/Aims: Primary and metastatic liver cancers are the leading causes of cancer-related death. Commensal bacteria play an important role in anti-tumor immunity, and then liver is continually exposed to gut microbes. However, the role of gut microbes in immune surveillance of liver tumors is still poorly understood. We conducted a study to evaluate the anti-tumor effects of vancomycin in combination with cytokine-induced killer (CIK) cells and programmed cell death 1 (PD-1) antibody in the metastatic liver cancer model.

Methods: A20 lymphoma cells ($1X10^6$) were injected intravenously into the BALB/c mice. Mice were randomly divided into 8 groups of eight mice and received the following treatments: 1) vehicle control, 2) CIK cells ($5X10^6$/mouse, i.v.), 3) PD-1 antibody (250 μg/mouse, i.p.), 4) CIK cells ($5X10^6$/mouse, i.v.) plus PD-1 antibody (250 μg/mouse, i.p.), 5) vancomycin (500 mg/kg, PO), 6) vancomycin (500 mg/kg, PO) plus CIK cells ($5X10^6$/mouse, i.v.), 7) vancomycin (500 mg/kg, PO) plus PD-1 antibody 250 μg/mouse, i.v.) and 8) all of three regimen for 2 weeks. The mice were euthanized at the termination of the experiments and liver samples were subjected to histological and immunohistochemical examination.

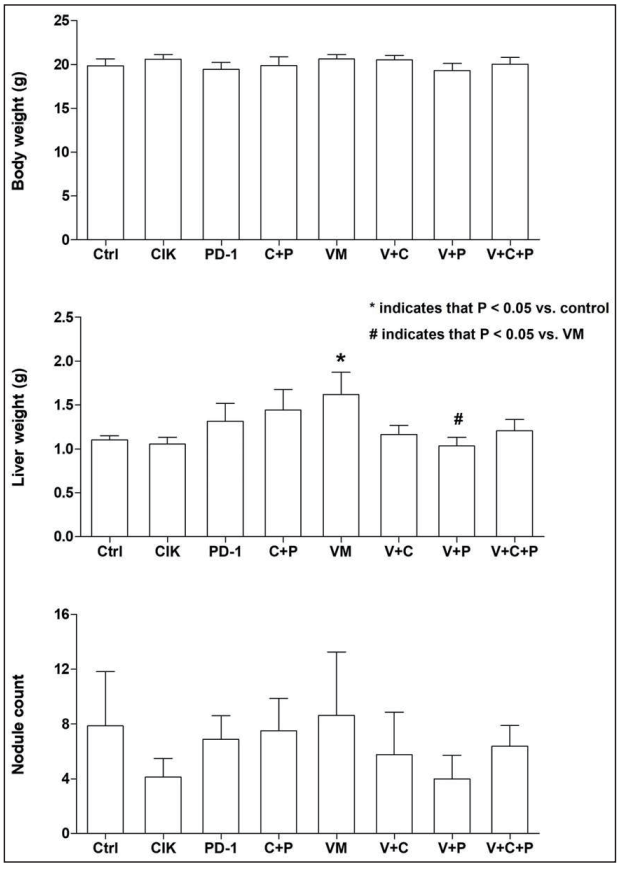

Figure 1. Mean and standard deviation of each weight and nodule count according to groups.
CIK, cytokine-induced killer cells; VM, vancomycin; PD-1, programmed cell death protein 1 antibody

Results: The vancomycin group showed significantly higher liver weight and nodule counts than other groups compared with control. Conversely, CIK cell group and vancomycin plus PD-1 antibody group showed significantly lower liver weight and nodule counts among those (Table 1).

Conclusions: Gut microbes can be used as a pharmabiotics to

promote the efficacy of immunotherapy such as CIK cells and PD-1 antibody. Further studies on immunologic enhancement mechanisms by gut microbes are needed.

Key words: Metastatic liver cancer, Gut microbes, CIK cells, PD-1 antibody

OP-076

TEAD2 as a Novel Prognostic Factor for Hepatocellular Carcinoma

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Department of Internal Medicine, Chungnam National University Hospital, Korea

Aims: TEA domain transcription factors (*TEAD*s) have an essential role in tumorigenesis. However, there is little data about *TEAD2* expression in hepatocellular carcinoma (HCC). We investigated the expression of TEA domain transcription factor 2 (*TEAD2*) in hepatocellular carcinoma (HCC) and whether it is correlated with patient prognosis in HCC.

Methods: We obtained mRNA expression data for Hippo pathway genes from 50 normal control and 377 patients with HCC from The Cancer Genome Atlas. We performed gene set enrichment, GeneNeighbors, ClassNeighbors, and survival analyses based on gene expression. We also performed real-time polymerase chain reaction and survival analysis using samples and clinical data from 46 patients with HCC.

Results: *TEAD2* and *VGLL4* mRNA expression was significantly higher in HCC than in controls; *TEAD2* mRNA expression was higher in advanced (TNM stage III/IV) than in early stages (TNM stage I/II). Survival analysis revealed that higher mRNA expression of *TEAD2* and *VGLL4* was correlated with poor overall survival (P=0.0067 and 0.051, respectively). Clinical analysis revealed an association between higher mRNA expression of *TEAD2* and poor recurrence-free survival (P=0.056). In gene set enrichment analysis, patients with higher *TEAD2* and *VGLL4* mRNA expression showed high epithelial-mesenchymal transition- and angiogenesis-related gene expression.

Conclusions: Increased *TEAD2* mRNA expression suggests the poor prognosis of patients with HCC. TEAD2 shows potential as a prognostic factor for HCC and novel therapeutic target.

Keywords: TEAD2, Hepatocellular carcinoma, Prognosis

OP-077

Hsa_circ_0005986 as a Prognostic Biomarker in Hepatocellular Carcinoma

Se Young Jang[1*], Gyeonghwa Kim[2*], Soo Young Park[1], Young-Oh Kweon[1], Yu Rim Lee[2], Jongwon Seo[1], Young Seok Han[3], JaRyung Han[3], Heon Tak Ha[3], Jae Min Chun[3], Eunhye Lee[2], Sumin Im[2], Jae Kyoung Seo[2], Jung Gil Park[4], Hye Won Lee[5], Won Young Tak[1], and Keun Hur[2]

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Aims: Circular RNAs (circRNAs), a class of endogenous RNAs, have been found to interact with microRNAs (miRNAs) or other molecules and regulate gene expression at the transcriptional or posttranscriptional level. Circular RNAs have drawn attention to become potential biomarkers for cancers due to resistance to RNases. The aim of the study is to analyze the expression of hsa_circ_5986 in hepatocellular carcinoma (HCC) and to investigate its clinical significance.

Methods: We analyzed clinical tissue samples from 162 patients who diagnosed as HCC at Kyungpook National University Hospital. RNAs were extracted from tissue samples according to the Trizol instructions. Circular RNA-specific primers were designed on the junction site, not linear RNA. Circular RNA expression levels were evaluated by quantitative real-time PCR. The association of hsa_circ_5986 expression with clinicopathological features and the survival were statistically analyzed.

Results: The mean age of the patients was 60 years (range: 18–88 years), and the majority were male (n=139, 85.8%). The Child-Turcotte-Pugh (CTP) classes were class A for 138 (85.2%) patients and class B for 22 (13.6%) patients. Seventy-three cases of HCC were stage I or II and 89 cases were stage III or IV, according to the TNM staging AJCC UICC 8th edition. We revealed that the expression level of hsa_circ_0005986 in hepatocellular carcinoma was decreased according to the cancer stage (P<0.01). In addition, the higher expression of hsa_circ_0005986 was associated with better overall survival (P<0.01, figure A) and progression-free survival (P=0.05, figure B).

Conclusions: Hsa_circ_0005986 can be a potential prognostic biomarker for predicting survival in HCC patients.

Keywords: Circular RNA, Hepatocellular carcinoma, Survival, Biomarker

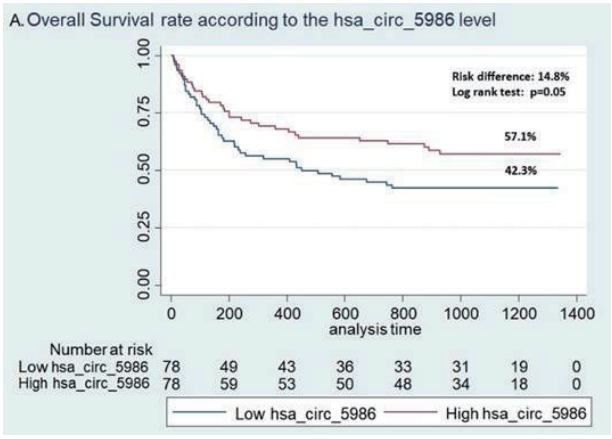

Figure A

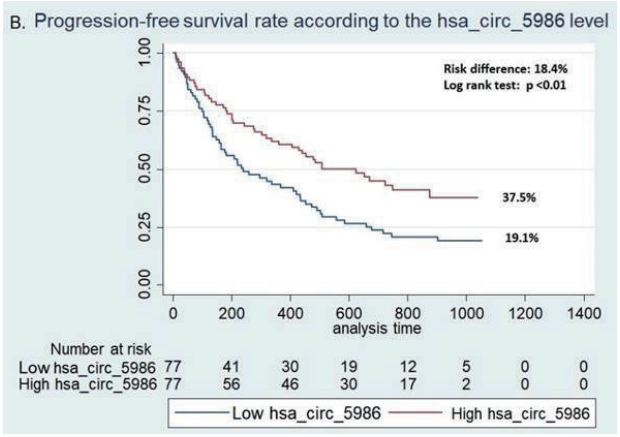

Figure B

[Group 5] June 22, 2019 | 13:20-14:20

Liver Cancer,Clinical

OP-078

Prognostic Value of Alpha-Fetoprotein in Patients Who Achieved Complete Response to Transarterial Chemoembolization for Hepatocellular Carcinoma

Jae Seung Lee[1], Wonseok Kang[3], Dong-Hyun Sinn[3], Moon Seok Choi[3], Geum-Youn Gwak[3], Yong-Han Paik[3], Joon Hyeok Lee[3], Kwang Cheol Koh[3], Seung Woon Paik[3], Hwi Young Kim[4], Tae Hun Kim[4], Kwon Yoo[4], Yeonjung Ha[5], Young Eun Chon[5], Mi Na Kim[5], Joo Ho Lee[5], Seong Gyu Hwang[5], Soon Sun Kim[6], Hyo Jung Cho[6], Jae Yoon Cheong[6], Sung Won Cho[6], Seung Ha Park[7], Nae-Yun Heo[7], Young Mi Hong[8], Ki Tae Yoon[8], Mong Cho[8], Jung Gil Park[9], Min Kyu Kang[9], Soo Young Park[10], Young Oh Kweon[10], Won Young Tak[10], Se Young Jang[10], Beom Kyung Kim[1,2], Jun Yong Park[1,2], Do Young Kim[1,2], Sang Hoon Ahn[1,2], Kwang-Hyub Han[1,2], Seung Up Kim[1,2*]: The Korean TACE Study Group

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Aims: The prognostic values of alpha-fetoprotein (AFP) in patients with hepatocellular carcinoma (HCC) are well-known. We investigated whether AFP is prognostic in patients with HCC who achieved radiological complete response (R-CR) after trans-arterial chemoembolization (TACE).

Methods: Between 2005 and 2018, 917 patients with HCC (588 treatment-naïve [TN-HCC] and 322 with recurrent HCC after curative resection [R-HCC]) who achieved R-CR after TACE (index date), based on the modified RECIST criteria, were recruited. AFP response was defined as the percentage of baseline AFP and AFP at R-CR.

Table 1.

Multivariate analysis for progression-free survival after achieving CR		
Variables	Multivariate	
	P value	Odds ratio (95% CI)
Total		
BCLC B/C vs. 0/A	0.025	1.298 (1.034-1.630)
Multiple tumors	0.001	1.387 (1.152-1.670)
Baseline AFP > 20 ng/mL	0.597	1.055 (0.866-1.285)
AFP at CR > 20 ng/mL	0.035	1.281 (1.017-1.612)
Albumin at CR	0.053	0.858 (0.735-1.002)
Naïve HCC		
BCLC B/C vs. 0/A	0.031	1.387 (1.030-1.870)
Multiple tumors	0.430	1.105 (0.862-1.416)
Baseline AFP > 20 ng/mL	0.416	1.110 (0.863-1.429)
AFP at CR > 20 ng/mL	0.043	1.349 (1.010-1.802)
Albumin at CR	0.077	0.840 (0.692-1.019)
Recurrent HCC		
BCLC B/C vs. 0/A	0.371	1.175 (0.825-1.675)
Multiple tumors	<0.001	1.892 (1.411-2.537)
Baseline AFP > 20 ng/mL	0.759	1.052 (0.759-1.458)
AFP at CR > 20 ng/mL	0.540	1.128 (0.768-1.656)
Albumin at CR	0.383	0.885 (0.673-1.164)

Table 2.

Multivariate analysis for overall survival after achieving CR		
Variables	Multivariate	
	P value	Odds ratio (95% CI)
Total		
Age > 70	0.004	1.443 (1.123-1.854)
Multiple tumors	0.002	1.405 (1.137-1.737)
Baseline AFP > 20 ng/mL	0.007	1.467 (1.112-1.936)
Bilirubin at CR	<0.001	1.401 (1.220-1.608)
AFP at CR > 20 ng/mL	0.666	0.940 (0.709-1.246)
Progression free survival	<0.001	0.977 (0.971-0.982)
Naïve HCC		
Age > 70	0.036	1.375 (1.021-1.853)
Multiple tumors	0.006	1.423 (1.107-1.829)
Baseline INR	0.029	5.052 (1.175-21.715)
Baseline AFP > 20 ng/mL	0.001	1.738 (1.249-2.419)
AFP at CR > 20 ng/mL	0.113	0.764 (0.548-1.006)
Progression free survival	<0.001	0.980 (0.974-0.986)
Recurrent HCC		
Multiple tumors	0.082	1.436 (0.956-2.157)
BCLC B/C vs. 0/A	0.439	1.214 (0.743-1.985)
Baseline bilirubin	<0.001	1.420 (1.180-1.709)
AFP at CR > 20 ng/mL	0.115	1.408 (0.921-2.154)
AFP response (%)	0.044	1.003 (1.000-1.005)
Progression free survival	<0.001	0.963 (0.950-0.977)

Results: The median age of patients in TN-HCC (433 male) and those in R-HCC (277 male) was 62.2 and 59.8 years, re-

spectively. During the follow-up period, 390 (66.3%) in TN-HCC and 253 (78.6%) in R-HCC experienced recurrence. In addition, 304 (51.7%) in TN-HCC and 125 (38.8%) in R-HCC died. The median progression-free survival (PFS) in TN-HCC and R-HCC groups was 17.1 and 15.5 months, respectively, whereas the median overall survival (OS) was 56.4 vs. 90.4 months, respectively. In TN-HCC group, AFP at R-CR >20 ng/mL (hazard ratio [HR=1.349]) and BCLC stage B and C (HR=1.387) independently predicted the shorter PFS (all P<0.05), whereas only multiple tumors independently predicted the shorter PFS in R-HCC group (HR=1.892, P<0.001). In TN-HCC group, baseline AFP > 20 ng/mL (not at R-CR) independently predicted shorter OS (HR=1.738), together with age > 70 years (HR=1.375), multiple tumors (HR=1.423), prothrombin time at baseline (HR=5.052) and shorter PFS (HR=0.980) (all P<0.05). In R-HCC group, AFP response independently predicted shorter OS (HR=1.003), together with higher total bilirubin level (HR=1.450) and shorter PFS (HR=0.963) (all P<0.05).
Conclusions: AFP values at R-CR and at baseline were independently predictive of recurrence and mortality in treatment-naïve patients after TACE, respectively. Thus, AFP should be used for more detailed risk stratification even after achieving R-CR after TACE.
Keywords: Hepatocellular carcinoma, Tumor marker, Recurrence, Overall survival

OP-079

Undetectable Viral DNA after Curative Surgery Predicts Favorable Survivals in Patients with Hepatitis B-Related Hepatocellular Carcinoma

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Aims: Recent studies showed increased hepatocellular carcinoma (HCC) recurrence after curative resection in patients with a high serum level of hepatitis B virus (HBV)-DNA at the time of surgery. However, the relationship between tumor recurrence and antiviral response to therapy is still unclear. In this study, we aimed to correlate postoperative viral DNA levels with posthepatectomy long-term survivals in patients with HBV-related HCC.
Methods: A retrospective study was conducted on patients who underwent liver resection between Jan 2003 to Dec 2017 at Seoul St. Mary's Hospital. The HBV-DNA titer was determined between month 6 and 12 after surgery, as well as long-term tumor recurrence and overall survivals were determined.
Results: Of 320 patients who underwent liver resection and whose baseline and follow-up HBV DNA levels were determined, 225 patients received antiviral treatment. At a median follow-up of 42.1 months, 125 patients (39%) had developed HCC recurrence and 70 patients (22%) had died or underwent salvage liver transplantation. The median time to recurrence was 27.2 months. Among the enrolled patients, 251 (78%) showed undetectable HBV DNA level, 34 (11%) showed low levels of HBV DNA detection (<1000 copies/mL), and 35 (11%) showed high levels of serum HBV DNA (≥1000 copies/mL). There was no significant difference between the two groups of patients who received antiviral treatment or not for either transplantation-free or disease-free survival. Furthermore, baseline HBV DNA level (high, ≥10000 copies/mL; low, <10000 copies/mL) was not associated with postoperative survival outcomes. On the other hand, after comparing survival outcomes between patients by their postoperative serum HBV DNA level, we confirmed that undetectable HBV DNA was a significant protective factor of both disease-free survival (P=0.013) and transplantation-free survival (P=0.002). On multivariate analyses, undetectable HBV DNA was still a significant factor of both disease-free survival (HR = 0.646, 95% CI, 0.438-0.955, P=0.028) and transplantation-free survival (HR = 0.393, 95% CI, 0.237-0.654, P<0.001).
Conclusions: Undetectable viral DNA after curative surgery predicts favorable survivals in patients with HBV-related HCC.
Keywords: Hepatocellular carcinoma, Hepatitis B virus, Antiviral treatment, Recurrence

OP-080

Prognosis and Survival Outcomes According to Body Mass Index in Hepatocellular Carcinoma Patients: An Analysis of a Nationwide Cancer Registry Database

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Aims: Body mass index (BMI) is a value derived from the weight and height of individual, and is known to be closely related to the prognosis and mortality of various disease. The aims of our study is to evaluated the differences of post-treatment overall survival (OS) according to BMI in the patients with hepatocellular carcinoma (HCC), and to determine the meaning of BMI in these patients.
Methods: The archived records of 10,578 HCC patients registered at the Korean Central Cancer Registry from 2008 through

2014 were retrospectively analyzed. In this registry, we selected Barcelona Clinic Liver Cancer (BCLC) 0, A, or B staged HCC patients (n=4,977). We compared normal weight (BMI 18.5-24.9 kg/m^2, n=1,790) and overweight (BMI 25-29.9 kg/m^2, n=1,790) patients after propensity score matching (PSM), and analysed the difference of OSs of these patients according to the treatment method.

Results: Among a total of 4,977 HCC patients, 151(3.0%), 3,014 (60.6%), 1,607 (32.3%), and 205 (4.1%) patients had BMI of underweight, normal, overweight, and obesity, respectively. HCC patients showed good prognosis in the order of overweight, normal, obesity, and underweight. However, comparing normal and overweight in HCC patients after PSM, there was no significant difference in survival rate between two groups (*P*=0.153). In separate analyses of males and females, the overweight had better prognosis than the normal body weight in male (*P*=0.014), but there was no significant difference in the OS between two groups in females (*P*=0.156). Overweight patients showed better OS in Transarterial Chemoembolization (TACE) treatment (*P*=0.039) compared to normal body weight, but not in surgical resection (*P*=0.618), radiofrequency ablation (*P*=0.553), or sorafenib (*P*=0.241).

Conclusions: In patients with HCC of BCLC 0-B, overweight patients showed good prognosis, but there was no significant difference between overweight and normal body weight after PSM. However, unlike females, males showed better prognosis in the case of overweight, especially TACE treated patients. Our results carefully suggest that the meaning of normal BMI may be different between males and females in the patients with HCC.

Keywords: Gender difference, Treatment in overweight HCC patients

OP-081

Availability of Tumor Markers in Patients with Pretreatment State of Hepatocellular Carcinoma

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Aims: To get information about differential diagnosis and clinical assessment. we evaluated quantitative changes of tumor markers (AFP, PIVKA-II) according to size, morphologic changes & clinical courses of tumor.

Methods: Medical records of 566 patients with hepatocellular carcinoma (HCC) were reviewed from 2009, April to 2019, March. 168 patients were excluded due to past anticancer management of other hospital, unconfirmed state, unavailability of both tumor marker within 6 months. Total 398 patients were enrolled. Age of cancer diagnosis, etiologic factor, metastasis or portal vein invasion, tumor size, morphology (single or multinodular, infiltrative, mass form), AFP & PIVKA-II were checked at time of HCC diagnosis. Size was classified as under 3 cm, 3~5 cm and over 5 cm. AFP & PIVKA-II were classified as under normal limit, normal limit~100, 100~1000, over 1000. PIVKA/AFP ratio is calculated for assessment.

Results: Each results were described as followed tables. Under 3 cm, both and each tumor marker's availability for diagnosis were only 40~50%. But according to tumor size above 3 cm, positive predictive value of tumor markers were increased. Especially PIVKA-II were more useful in larger size (> 5 cm). If we used both marker in larger size HCC (> 5 cm), only 2.5% showed normal tumor marker ranges. AFP levels were not depended on tumor morphology, but PIVKA-II levels were changed to morphology. Infiltrative form showed highest PIVKA-II, and multinodular form showed lowest PIVKA-II. So PIVKA/AFP ratio (≥5 & 100) showed differences as infiltrative (77%, 43%), mass (66%, 28%), and multinodular (59%, 17%) forms.

Table 1. Tumor marker changes according to HCC size

	AFP	PIVKA	AFP	PIVKA	AFP	PIVKA	AFP	PIVKA	both marker
	<10	<40	10~100	40~100	100~1000	100~1000	≥1000	≥1000	normal range
< 3 Cm	60%	65%	23%	17%	17%	15%	0%	3%	48.5%
3~5 Cm	40%	29%	27%	28%	19%	37%	14%	6%	12.2%
> 5 Cm	24%	10%	21%	6%	43%	29%	12%	55%	2.5%

Table 2. Tumor marker changes according to HCC morphology

	AFP	PIVKA	AFP	PIVKA	AFP	PIVKA	AFP	PIVKA	both marker
	<10	<40	10~100	40~100	100~1000	100~1000	≥1000	≥1000	normal range
infiltrative form	17%	7%	22%	9%	43%	23%	18%	61%	1.8%
mass form	35%	13%	25%	15%	30%	34%	10%	38%	3.3%
multinodular form	31%	25%	22%	13%	32%	36%	15%	26%	9.4%

Table 3. PIVKA/AFP ratio according to tumor morphology

PIVKA/AFP ratio	< 1	1~5	≥ 5 (>100)
infiltrative form	16%	7%	77% (43%)
mass form	18%	16%	66% (28%)
multinodular form	23%	19%	59% (17%)

Keywords: Hepatocellular carcinoma, AFP, PIVKA-II, Classification

OP-082

Validation of AJCC 8th Staging System in Patients with Resected Hepatocellular Carcinoma

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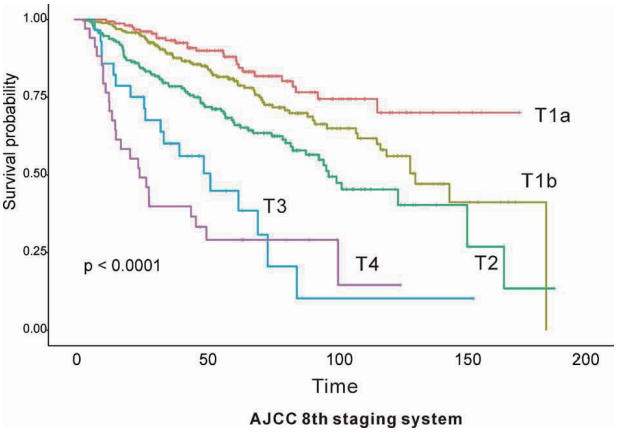
Aims: The American Joint Committee on Cancer (AJCC) 8th edition staging manual introduced several significant changes to the staging system for hepatocellular carcinoma (HCC). Our study aimed to validate the latest staging system and compare the performance to the previous 7th edition.

Methods: We retrospectively reviewed database of 698 patients with pathologically confirmed stage I-III HCC between year 2003 and 2016 from three institutes. Overall and cancer-specific survival (OS, CSS) analysis were performed using Kaplan-Meier method and compared using log-rank tests. The Harrell concordance index (c index) and Akaike information criterion (AIC) were calculated to compare prognostic powers.



Results: A total 698 patients who had undergone hepatic resection were available for the analysis. The cohort were comprised of T1a (22.5%), T1b (38.4%), T2 (30.1%) T3 (4.2%) T4 (4.9%) stages according to AJCC 8th staging system while T1 (58.3%), T2 (32.7%), T3a (4.2%) T3b (2.9%) T4 (2%) stages according to AJCC 7th staging system. When the AJCC 8th staging system was applied for OS, p-values of pairwise comparisons among all T stages differed significantly (P<0.005) except for T3 and T4 (P=0.137). The AIC value of OS 8th edition staging system were lower than 7th edition (2493.85 and 2500.19, respectively) while c-indices were higher (0.63 and 0.66, respectively) (P=0.005). The AJCC 8th system also performed better for CSS, the AIC value for the 8th edition was 1638.27 while it was 1651.96 for 7th edition and the c-indices were 0.7 and 0.65, respectively (P<0.001).

Conclusions: The latest staging system provided more accurate prognostic information than the previous edition. However, prognostic power of the new staging system for discrimination of T3 and T4 stage should be further validated in a larger cohort.

Keywords: AJCC, Hepatocellular carcinoma, Survival, Prediction

OP-083

HCV Eradication Using Direct-Acting Antivirals Improve Treatment Outcomes in Patients with HCV-Related HCC Treated with TACE: A Multi-Center Retrospective Cohort Study

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Aims: Direct-acting antiviral (DAA) treatment effectively eradicate chronic hepatitis C virus (HCV) infection. This multicenter, retrospective, cohort study investigated whether HCV eradication using DAA treatment improve treatment outcomes in patients with HCV-related hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE).

Methods: Between 2006 and 2017, patients with HCV-related HCC who achieved sustained virological response (SVR) and treated with TACE within 12 months were recruited. The study population was stratified into two groups: 1) no antiviral treatment (AVT) (n=297 [88.9%], Control group), 2) SVR by pegylated interferon-based AVT (n=10 [3.0%], PR group), and 3) SVR by DAA (n=27 [8.1%], DAA group).

Results: The median age of the study population (244 men and 90 women) was 68.2 years. A total of 297 (88.9%), 10 (3.0%), and 27 (8.1%) patients were stratified into Control, PR, and DAA groups, respectively. During the follow-up period, 251 (75.1%) patients experienced progressive diseases (PD), whereas 230 (68.9) patients were dead. On multivariate analysis, DAA group was independently associated with a reduced risk of mortality (hazard ratio [HR]=0.510, 95% confidence interval [CI] 0.284-0.917, P=0.024) when compared to Control group (reference), whereas cirrhosis (HR=2.787), higher alpha-fetoprotein level (HR=1.000), and maximal tumor size (HR=1.140) were independently associated with an increased risk of PD (all P<0.05). The progression-free survival (PFS) of DAA group was significantly higher than that of Control group (P=0.021 by log-rank test), but similar to that of PR group (P=0.158 by log-rank test). On multivariate analysis, DAA group was independently associated with a reduced risk of mortality (HR=0.350, 95% CI 0.129-0.948, P=0.039) when compared to Control group (reference), whereas older age (HR=1.030), larger maximal tumor size (HR=1.066), multiple tumor (HR=1.619), segmental portal vein thrombosis (HR=2.620), cirrhosis (HR=1.553), and higher alpha-fetoprotein level (HR=1.000) were independently associated with an increased risk of mortality (all P<0.05). The overall survival of DAA group was significantly higher than that of Control group (P=0.006 by log-rank test), but similar to that of PR group (P=0.212 by log-rank test).

Conclusions: DAA treatment prolongs PFS and overall survival in patients with HCV-related HCC treated with TACE.

Keywords: Transarterial chemoembolization, direct-acting antiviral, Hepatitis C, Outcome

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Liver Cancer,Clinical

OP-084

The Study about Immunologic Markers Predicting Efficacy of Locoregional Therapy for Hepatocellular Carcinoma

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Aims: We aimed to investigate changing pattern of immunologic factors after locoregional therapy (LRT) (radiotherapy and transarterial chemoembolization and radiofrequency ablation) for hepatocelluar carcinoma and discover predictive marker of response of LRT.

Methods: Eligible HCC patients were recruited in Dongnam Institute of Radiological & Medical Sciences from July 2017 to December 2017. We performed blood sampling of three times (baseline, 1 day, 1 week, 4 weeks after LRT) and analyzed immunologic markers as followings; CD4+, CD8+, regulartory T cell (Treg), monocyte and granulocyte myeloid derived suppressor cell (mo-MDSC & g-MDSC) in all enrolled patients. Response assessment using both RECIST and modified RECIST criteria were performed after 1 month & 3 months after initial LRT.

Results (IV) – 1 mo Response Anaylsis (13 patients)

- **PD: 5 patients (2 EHM, 3 New lesion), nonPD: 8 patients (7 CR, 1 SD)**

	CR (7)	PD (5)	p-value
Tumor marker			
AFP	28.71 ± 28.41	974.96 ± 1769.229	0.089
PIVKA	207.56 ± 236.58	64.4 ± 49.93	0.11
Immunologic marker			
Treg_PosTx(1)	7.53 ± 1.41	4.76 ± 0.86	0.001
Treg_PostTx(2)	5.138 ± 2.285	7.61 ± 2.65	0.091
	CR (7)	PD (2 EHM)	p-value
Tumor marker			
AFP	28.71 ± 28.41	2388.75 ± 2420.07	0.007
PIVKA	207.56 ± 236.58	101 ± 31.11	0.281
Immunologic marker			
Treg_PosTx(1)	7.53 ± 1.41	4.49 ± 0.78	0.011

Results (IV) – 3 mo Response Anaylsis (13 patients)

- **PD: 10 patients (3 EHM, 7 New lesion), nonPD: 3 patients (All CR)**

	CR (3)	PD (10)	p-value
Tumor marker			
AFP	55.83 ± 50.35	648.35 ± 1310.59	0.232
PIVKA	28.63 ± 8.17	238.4 ± 253.9	0.096
Immunologic marker			
CD8_Baseline	31.86 ± 7.34	19.71 ± 7.09	0.012
	CR (3)	PD (3 EHM)	p-value
Tumor marker			
AFP	55.83 ± 50.35	1593.4 ± 2196.8	0.146
PIVKA	28.63 ± 8.17	200.33 ± 173.45	0.08
Immunologic marker			
Treg_PosTx(1)	6.37 ± 0.31	4.49 ± 0.78	0.014
mo-MDSC_PostTx(1)	3.57 ± 1.67	0.44 ± 0.01	0.043

Results: Thirteen patients were enrolled in the study. Eleven patients were male, two patients were female. The median age was 66 years (range, 48-78) and all patients were in ECOG performance status 0-1. Ten patients had Child A cirrhosis and 5 patients were in BCLC A stage, 6 patients in BCLC B, 2 patients in BCCL C. The median value of AFP is 40.2 ng/mL (range, 2.6-4100), that of PIVKA is 79 mAU/mL (range 12-695). The median size of tumor were 2.0 cm (range, 0.8-11.2). Nine patients had multiple tumor. The level (%) of mo-MDSC at 1 day after LRT was significantly increased than baseline (7.09 ± 5.85 versus 3.51 ± 3.17, p value = 0.032). The tendency was showed that the level of CD4+, CD8+, CD4+/CD8+ ratio were maximized at 1 week after LRT and those of g-MDSC were maximized at 1 day after LRT. At 1 months after LRT, 4 patients had progressive disease (PD) and 8 patients had complete response (CR). At 3 months after LRT, 10 patients had PD (2 lung metastasis, 8 intrahepatic new lesions) and 3 patients had CR. The level (%) of Treg at 1 day after LRT was significantly increased in patients with CR than PD in 1 months response assessment (7.53 ± 1.41 versus 4.76 ± 0.86, p value = 0.001) and that of Treg and mo-MDSC were significantly increased in patients with CR than lung metastasis in 3 months response assessment (Treg; 6.37 ± 0.31 versus 4.49 ± 0.78, p value = 0.014, mo-MDSC; 3.57 ± 1.67 versus 0.44 ± 0.01, p value = 0.043). The level (%) of baseline CD8+ T cell was significantly increased in patients with CR than PD in 3 months response assessment (31.86 ± 7.34 versus 19.71 ± 7.09, p value = 0.012).

Conclusions: Our study suggests that our investigation about maximal immunogenic period after LRT may be meaningful in the era of immunotherapy and the immunologic markers maybe predictive tool of treatment response of LRT of HCC. Further well controlled, large scaled study to prove survival benefit using our markers is recommended.

Keywords: Hepatocellular carcinoma, Locoregional therapy, Immunologic marker

OP-085

Development of a New Nomogram Including Neutrophil-to-Lymphocyte Ratio to Predict Survival in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

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Aims: The neutrophil-to-lymphocyte ratio (NLR) has recently been reported to predict the prognosis of hepatocellular carcinoma (HCC). We explored whether NLR predicted the survival

of patients with HCC undergoing transarterial chemoembolization(TACE), and developed a predictive model.

Methods: In total, 1,697 patients with HCC undergoing TACE as first-line therapy at two university hospitals were enrolled (derivation set n=921,internal validation set n=395,external validation set n=381). The tumor *S*ize, tumor *N*umber, *A*FP level, *V*ascular invasion, *C*hild-Pugh score, *O*bjective *R*esponse after TACE, and *N*LR, selected as predictors of overall survival (OS) via multivariate Cox's regression model, were incorporated into a 14-point risk prediction model (SNAVCORN score).

Results: The time-dependent areas under the receiver-operating characteristic curves for OS at 1, 3, and 5 years predicted by the SNAVCORN score were 0.812, 0.734, and 0.700 in the derivation set. Patients were stratified into three risk groups by ABCRN score (low,0–4; intermediate,5–9; high,10–14). Compared with the low-risk group, the intermediate-risk [HR 3.10, *P*<0.001] and high-risk (HR 7.37, *P*<0.001) groups exhibited significantly greater mortality.

Conclusions: The prognostic performance of the SNAVCORN score including NLR in patients with HCC treated with TACE was remarkable, much better than those of the conventional scores. The SNAVCORN score will guide future HCC treatment decisions.

Table 2. Prognostic factors for overall survival and risk score calculation in the derivation cohort (n=921)

Variables	Uni	Multi			
	P-value	Adjusted HR(95% CI)	β-coefficient	SNAVCORN Risk score	
tumor Size	<0.001	<0.001			
≤3cm			1.000		0
>3cm			1.555 (1.252-1.932)	0.441	1
tumor Number	<0.001	<0.001			
≤3			1.000		0
>3			1.752 (1.354-2.268)	0.561	2
AFP	<0.001	0.032			
<200			1.000		0
≥200			1.291 (1.022-1.629)	0.255	1
Vessel invasion	<0.001	<0.001			
No			1.000		0
Present			2.272 (1.793-2.879)	0.821	3
Child-Pugh score	<0.001	<0.001			
5			1.000		0
6			1.483 (1.195-1.840)	0.394	2
7-8			1.903 (1.412-2.563)	0.643	3
9			2.852 (1.401-5.806)	1.048	4
Objecvtive Response	<0.001	<0.001			
CR+PR			1.000		0
SD+PD			1.663 (1.267-2.182)	0.508	2
NLR ratio	<0.001	0.015			
<5			1.000		0
≥5	<0.001	0.015	1.380 (1.064-1.789)	0.322	1

AFP, alpha-feto protein; CR, complete reponse; PR, partial response; SD, stable disease; PD, progressive disease; NLR, neutrophil-to-lymphocyte ratio.

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Neutrophil-to-lymphocyte ratio, Risk-prediction model

OP-086

Outcome and Safety of Second or Third-Line Nivolumab Treatment in Real Life: A Single Center Experience

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Aims: Nivolumab is an immune checkpoint inhibitor approved for the second-line therapy for advanced HCC. The aim of this study is to describe our experience with nivolumab in patients who have progressed on or been intolerant of prior sorafenib.

Methods: Forty-two patients with advanced HCC receiving nivolumab (3mg/kg intravenously every 2 weeks) were enrolled between October 2017 and November 2018. Assessment of response was based on the Immune-Modified Response Evaluation Criteria In Solid Tumors (iRECIST) and RECIST version 1.1 every 8 weeks.

Results: The median age of patients was 61 years. Portal vein invasion and extrahepatic spread was present in 38% and 76%, respectively. The median duration of nivolumab treatment was 76 days. Six out of 42 patients are on treatment, while 36 patients stopped treatment because of disease progression, serious toxicity, treatment refusal and discontinuance after achieving a complete response (CR). For evaluating tumor response, one showed CR; 7 (16.7%) partial response; 9 (21.4%) stable response; 1 immune unconfirmed progression and 24 (57.1%) immune confirmed progression. Three patients were continued to receive nivolumab after first response of progression due to a possibility of pseudo-progression and finally confirmed as progressed disease. Median duration of response was 80 days. The 3- and 6-month disease control rate were 47.0% and 23.5%, respectively. Median OS was 242 days and median progression free survival (PFS) was 108 days. Survival rate and PFS rate at 6 months were 55.6% and 29.0%, respectively. Common adverse reactions included abdominal discomfort (29%), skin eruption or pruritus (24%), general weakness (14%), fatigue (10%). The grade 3 adverse events included hepatotoxicity, azotemia, hematochezia, hyperbilirubinemia, hypercalcemia, and pneumonitis.

Conclusions: In real life practice of a single center, nivolumab as an above second-line therapy appears to have meaningful efficacy and acceptable tolerability in patients with advanced HCC. Further follow-up studies are warranted.

Keywords: Advanced HCC, Nivolumab

OP-087

Effectiveness of Dose Reduction of Sorafenib on HCC Treatment: A Real Life Multicenter Data Analysis

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Aims: Currently, there is a lack of general agreement on sorafenib dosing. This study is a large real-life cohort study aiming to evaluate whether sorafenib dosing would affect patient outcomes.

Methods: A total of 782 patients treated with sorafenib between 2008 and 2017 were evaluated for sorafenib dosing. Sorafenib dose was recorded daily during admission by continuing number of remaining pills and questionaires during regular follow up for out-patients. Clinical outcome measures were analyzed according to dose modification. Primary outcomes were overall survival and time to progression.

Results: Median survival of patients was 5.2 months. In multivariate analysis, dose reduction had significant benefit on overall survival (*P*=0.019) and progression-free survival (*P*=0.034). In subgroup analysis, there were no significant difference in overall and progression-free survial between the 800-to-600 mg group and the 800-to-400mg group. Both hand-foot syndrome (*P*=0.049) and drug discontinuation due to adverse events (*P*=0.003) were more frequent in the 800-to-600 vs. 800-to-400 mg group. Dose reduction to 200 mg significantly reduced overall survival (*P*=0.014) and progression-free survival (*P*=0.025). Dose reduction significantly increased both medication duration (*P*<0.001) and cumulative dose (*P*<0.001). In subgroup analysis, the 800-to-400 mg group had significantly longer duration (*P*<0.001) and higher cumulative dose (*P*=0.02) than the 800 mg-maintained group. The benefits from dose reduction persisted in subgroup analysis of good responders.

Conclusions: In HCC patients treated with sorafenib, appropriate dose reduction may lead to longer overall and progression-free survival by increasing adherence coupled with higher cumulative dose. Based on our data, dose reduction of sorafenib from 800 mg to 400 mg rather than 600 mg is suggested. Dose reduction to 200 mg is not recommended.

Keywords: Sorafenib, Hepatocellular carcinoma, Dose reduction

OP-088

Serum Exosomal microRNA-10b-5p as a Potential Biomarker of Early Stage Hepatocellular Carcionoma

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Aims: There is no reliable serum biomarker for screening early Hepatocellular carcinoma (HCC). Exomal microRNA has been highlighted as promising cancer biomarker. This study aimed to find reliable serum biomarker of early HCC by using small RNA sequencing of HCC cell derived exosome (HEX).

Methods: Exosomes from human HCC cell lines (Hep3B and Huh-7) and immortalized normal hepatocyte cell line (THLE-2) were isolated and small RNAs were extracted. Differentially expressed exosomal microRNAs between HEX and normal hepatocyte were screened by using Ilumina Hiseq2000 deep sequencing. To select potential candidate of biomarker among the overexpressed microRNAs in HEX, TCGA data was analyzed. For validation of clinical usefullness of the exosomal microRNAs, RT-PCR was performed in the independent liver disease cohort including 18 normal control, 19 chronic hepatitis B (CHB) patients, 20 liver cirrhosis (LC) patients, 20 early stage HCC (modified UICC stage I), 19 advanced HCC patients (modified UICC stage III or IV).

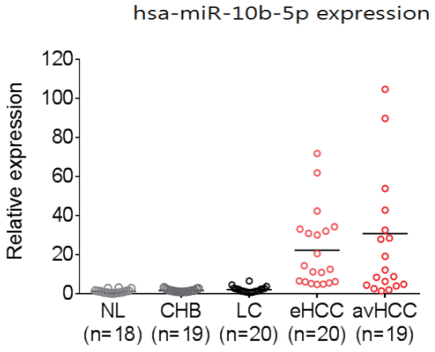

Figure 1

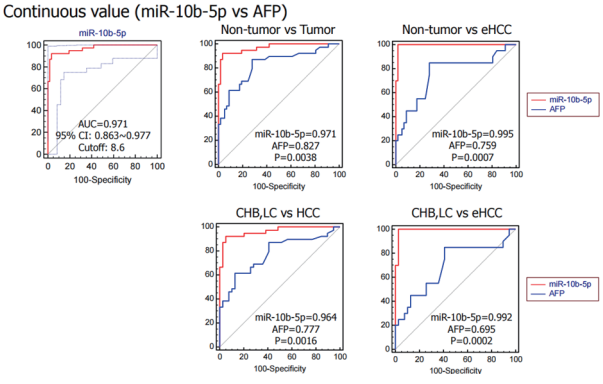

Figure 2

Results: A total of 49 overexpressed exosomal microRNA in HEX more than 1.5 folds compared to normal hepatocyte were identified. TCGA data was analyzed to select the candidate microRNAs among the 49 microRNAs. In the analysis of TCGA data, microRNA-10b-5p, microRNA-18a-5p, microRNA-215-5p, and microRNA-940 were identified as significantly overexpressed microRNAs in HCC tissue, and they also associated with HCC patient's prognosis. RT-PCRs of the 4 microRNAs were performed in the independent cohort for validation of clinical usefulness of the candidate biomarkers. As a result, serum exosomal microRNA-10b-5p was significantly overexpressed in early and advanced HCC patients compared to the patients with CHB or LC (Fig.1). In the comparison of area under the curve

(AUROC) for early HCC diagnosis, exosomal microRNA-10b-5p (AUROC=0.992) shows significantly higher diagnostic accuracy compared to AFP (AUROC=0.695). (*P*=0.0002) (Fig.2)

Conclusions: Serum exosomal microRNA-10b-5p is promising biomarker to detect early HCC.

Keywords: Hepatocellular carcinoma, Exosome, MicroRNA, Sequencing

OP-089

Multicenter Retrospective Analysis of the Efficacy of Regorafenib after Progression on Sorafenib with Hepatocellular Carcinoma

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Introduction: Regorafenib has been proved as 2nd line systemic therapy for hepatocellular carcinoma (HCC) patients with progression after sorafenib through 3 phase trial improving survival compared to placebo. Nevertheless, real-world data are needed to assess clinical outcomes in the practice. We analyzed the real-world data to assess clinical outcomes in the practice.

Methods: This study was a multicenter, non-comparative, retrospective cohort study. Between July 2017 and May 2019 in seven Korean institutions (Korea University College of Medicine, Chonnam National University Hwasun Hospital, Korea Cancer Center Hospital, Gangnam Severance Hospital, Soonchunhyang University Hospital), patients with HCC who had evidence of disease progression on sorafenib were eligible for inclusion in this study. A total of 133 Patients who received at least one dose of regroafenib were included in this analysis. Tumor response was assessed according to modified RECIST criteria. Kaplan - Meier method and Cox regression were used for survival analysis.

Results: Their median age was 60 years, and most patients (n=112, 84.2%) were male. Hepatitis B virus (n=91, 68.4%) infection was the most common etiology of HCC. Except for 2 patients (1.5%) with Child-Pugh B (n=1) and C (n=1), all patients were classified as Child-Pugh A at the time of initiation of regorafenib. 113 patients (84.9%) had extrahepatic metastasis, with the most common metastatic site being the lungs (n=77, 57.8%), followed by the bones (n=32, 24%), adrenal glands (n=11, 8.2%) and vascular invasion (n=56, 42.1%). We assessed a best response for 112 patients with at least one follow up imaging studies. Three patients (2.6%) achieved CR, and 11 patients (9.8%) achieved PR. Obsective response rate was 12%. SD and PD were the best responses in 25 (22.3%), and 71 (63.3%) patients, respectively. The disease control rate was was 32.1%. The median overall survival (OS) was 10.03 months, and the median progression-free survival (PFS) was 2.7 months. Four out of 8 variables were indentified statistically significant in univariate logistic regression analysis for OS and PFS. These 4 significant variables entered multivariate logistic regression analysis. As a result, There was an association with increased overall survival risk if the Child-pugh score was higher than 5 [OR (95% CI)=3.638 (1.797-7.361), *P*=0.000] or AFP was higher than 400 [OR (95% CI)=3.570 (1.731-7.361), *P*=0.001] and decreased OS risk if the Sorafenib TTP was above the median (3.7 mo) [OR (95% CI)=0.395 (0.195-0.803), *P*=0.01]. The risk of PFS decreases when Sorafenib TTP was above the median (3.7 mo) [OR (95% CI)=0.571 (0.376-0.869), *P*=0.009] and increases when HCC extent was more than half of liver [OR (95% CI) =1.683 (1.068-2.653), *P*=0.025].

Conclusions: Regorafenib was effective in patients with advanced HCC who progressed on first-line sorafenib in real-life setting consistent with the efficacy of the previous controlled clinical trial. TTP on first-line sorafenib, Child pugh score, AFP and HCC extent were independent predictor of the prognosis for regorafenib.

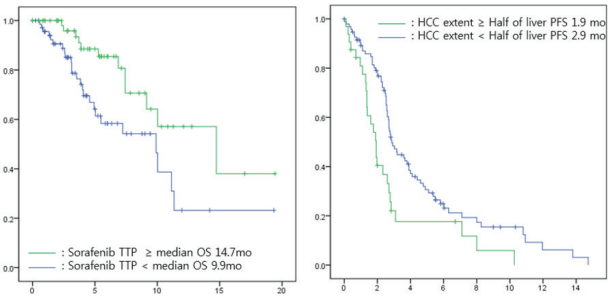

Figure 1. Kaplan-Meier curves for OS and PFS

Keywords: Hepatocellular carcinoma, Regorafenib, Sorafenib

[Group 7] June 22, 2019 | 13:20-14:20

Liver Cancer,Clinical

OP-090

Appraisal of Transarterial Chemoembolization Refractoriness in Patients with Hepatocellular Carcinoma

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Aims: In real-world practice, transarterial chemoembolization (TACE) has been widely used for treating hepatocellular carcinoma (HCC) beyond, as well as within, guideline recommen-

dations. Some guidelines defined TACE-refractoriness by consensus to encourage switching other treatment modalities. This study was to verify that two consecutive non-responses could be an optimal criterion for stopping rule for TACE.

Methods: This study evaluated 200 patients with HCC beyond the Milan criteria initially treated with on-demand TACE. TACE response was determined by mRECIST criteria using dynamic CT or MRI. Median follow-up duration was 23.9 months.

Results: The 200 patients consisted of 183 (91.5%) men and 17 (8.5%) women, of mean age 59.8 years. The mean size of the largest tumor was 6.8 cm, and 80 (40.0%) patients had ≥4 tumors. After the first TACE session, complete response, partial response, stable disease, and progressive disease were observed in 48 (24.0%), 87 (43.5%), 59 (29.5%), and 6 (3.0%) patients, respectively. Forty-five (22.5%) patients showed no objective response (OR) twice consecutively at any time during repeated TACE. Of these, 28 received subsequent TACE with an 10.7% of objective response rate. Patients without OR had poorer survival compared to patients achieved OR after repeated TACE. Multivariable analysis showed that the size of the largest tumor >5 cm and high AFP of >200 ng/mL were significant factors associated with failure of OR twice after repeated TACE.

Conclusions: Repeated TACE without OR twice resulted in poor OR to subsequent TACE. Early transition to systemic therapy may be advocated in patients refractory to TACE.

Keywords: Hepatoceelular carcinoma, Transarterial chemoembolization, Objective response, Survival

OP-091

Validation of Prognostic Impact of ADV Score for Resection of Hepatocellular Carcinoma: An Analysis Using Nationwide Korea Liver Cancer Registry Database

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Aims: We validated the prognostic power of ADV score (alpha-fetoprotein- des-γ-carboxyprothrombin (DCP)-tumor volume score: (AFP (ng/ml) x DCP [PIVKA-II] (mAu/mL) x tumor volume (mL): expressed in $\log_{10}$) for predicting risk of hepatocellular carcinoma (HCC) recurrence after hepatic resection (HR).

Methods: This study included 1526 patients who underwent HR for solitary HCC between 2008 and 2012 and followed up until December 2016. They were registered to the Korean cancer registry database. We selected the only patients who underwent HR as the first treatment of HCC.

Results: During follow-up, 349 patients (22.8%) died due to HCC recurrence. Distribution of ADV scores were < 2log in 25 (1.6%), 2-3log in 175 (11.4%), 3-4log in 318 (20.8%), 4-5log in 309 (20.2%), 5-6log in 240 (15.7%), 6-7log in 156 (10.2%), 7-8log in 113 (7.4%), 8-9log in 93 (6.1%) and >9log in 97 (6.4%). Patient survival rate was closely correlated with ADV score (P<0.001). 5-year patient survival rate was around 90% in ADV score of 2log, 85% in ADV score of 4log, 75% in ADV score of 6log, 60% in ADV score of 8log and 50% in ADV score of >8log (P<0.001). These ADV score-dependent prognostic stratification was quite well matched with the previously reported results from single center and multicenter studies.

Conclusions: Our results using a high-volume HCC cohort confirmed that ADV score is an integrated surrogate prognostic biomarker which can be reasonably applicable to the patients undergoing HR for HCC.

Keywords: Cohort, ADV score, Tumor marker, Resection

OP-092

Better Prediction of Outcomes by Response Evaluation Using the Modified RECIST Compared with the RECIST 1.1 in Patients with HCC Treated with Yttrium-90 Radioembolization

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Yonsei University College of Medicine

Background/Aims: The response evaluation criteria in solid tumours 1.1 (RECIST 1.1) have been commonly used for response evaluation of solid tumours including hepatocellular carcinoma (HCC). Because of the importance of the remaining 'viable cancer tissue' of HCC, the modified RECIST (mRECIST) have been adopted for HCC response evaluation. However, few studies have investigated which response evaluation method is better for predicting the treatment outcomes of HCC. Thus, we compared the performance of the RECIST 1.1 and mRECIST for predicting survival rates in patients with HCC treated with transarterial radioemoblisation (TARE) using Yttrium-90 (90Y).

Methods: Between 2012 and 2017, 102 patients with unresectable intrahepatic HCC treated with TARE were reviewed retrospectively. The RECIST 1.1 and mRECIST were used to evaluate the treatment responsiveness of HCC to TARE at 1, 3 and 6 months after TARE. A responder was defined as the sum of either a complete or partial response by each method.

Results: The median age of the study patients (92 males and 19 females) was 64.1 years. The median alpha-fetoprotein and des-gamma-carboxyprothrombin levels were 42.0 ng/mL and 1693.5 mAU/mL, respectively. The median maximal tumor size was 8.3 cm, and multiple tumours were observed in 41 (36.3%) patients. During the follow-up period (median 20.7 months), 21 patients (20.6%) died, with a median survival of 32.5 months. Using the mRECIST, the treatment responders at 1, 3 and 6 months following TARE showed significantly better survival rates compared with the non-responders (hazard ratio [HR]=5.736, log-rank P=0.008 at 1 month; HR=3.145, P=0.022 at 3 months, and HR=2.887, P=0.061 at 6 months). In contrast, using the RECIST 1.1, the treatment responders at 1, 3 and 6

months In contrast, using the RECIST, the treatment responders at 1, 3, and 6 months showed no statistical difference in survival from the non-responders (all P>0.05, log-rank test). According to multivariate analysis, non-responsiveness using mRECIST (HR=0.217, P=0.043 at 1 month; HR=2.874, P=0.05 at 3 months), as well as the serum albumin level, main portal vein thrombosis, and hepatic vein invasion, were independent predictors of mortality (all P<0.05).

Conclusions: Risk stratification should be assessed by response evaluation using mRECIST in patients with HCC treated with TARE. Further validation in a large cohort is required.

OP-093

Preoperative Transcatheter Arterial Chemoembolization for Surgical Resection of Huge Hepatocelluar Carcinoma (≥ 10 cm): A Multicenter Propensity Matching Analysis

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Aims: Surgical resection for hepatocellular carcinoma (HCC) is potentially curative, but long-term survival remains unsatisfactory. There is currently no effective neoadjuvant or adjuvant therapy for HCC. We sought to evaluate the impact of preoperative transcatheter arterial chemoembolization (TACE) on long-term prognosis after surgical resection of huge HCCs (≥ 10 cm).

Methods: Using a multicenter database, consecutive patients who underwent curative-intent resection for huge HCC without macrovascular invasion between 2004 and 2014 were identified. The association between preoperative TACE with perioperative outcomes, long-term overall survival (OS) and recurrence-free survival (RFS) was assessed before and after propensity score matching (PSM).

Results: Among the 377 enrolled patients, 88 patients (23.3%) received preoperative TACE. The incidence of perioperative mortality and morbidity was comparable among patients who did and did not undergo preoperative TACE (3.4% vs. 2.4%, *P*=0.704, and 33.0% vs. 31.1%, *P*=0.749, respectively). PSM analysis created 84 matched pairs of patients. In examining the entire cohort as well as the PSM cohort, median OS (overall cohort: 32.8 vs. 22.3 months, *P*=0.035, and PSM only: 32.8 vs. 18.1 months, *P*=0.023, respectively) and RFS (12.9 vs. 6.4 months, *P*=0.016, and 12.9 vs. 4.1 months, *P*=0.009, respectively) were better among patients who underwent preoperative TACE versus patients who did not. After adjustment for other confounding factors on multivariable analyses, preoperative TACE remained independently associated with a favorable OS and RFS after resection of huge HCC.

Conclusions: Preoperative TACE did not increase perioperative morbidity or mortality, yet was associated with an improved OS and RFS after liver resection of huge HCC.

OP-094

Optimal Timing of Radiotherapy for Incomplete Transarterial Chemoembolization in BCLC Stage B Hepatocellular Carcinoma

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Aims: Efficacy of radiotherapy (RT) after incomplete transarterial chemoembolization (TACE) has been documented through many reports. However, optimal timing of RT still remains unanswered. This study was to investigate the optimal time to start RT for incomplete TACE in patients with BCLC stage B hepatocellular carcinoma (BCLC-B HCC).

Methods: During 2001-2016, 112 patients with BCLC-B HCC were treated with RT for 116 lesions after incomplete TACE. Through the medical records review, the time-interval between the last TACE and the start of RT was examined. The optimal cut-off of time-interval to maximize the difference in local failure-free rate (LFFR) was determined using the maximally selected rank statistics.

Results: In total patients, the median overall survival was 17.9 months. The median age was 59 years (range, 34–83 years), the median tumor size was 6 cm (range, 1–20 cm), and the median number of the tumor was 1 (range, 1–9). The median number of TACE on the target lesion before RT was 2 (range, 1–7). We found 5 weeks as the optimal cut-off value of time interval, which we classified patients groups as consolidation RT (cRT) for earlier than 5 weeks and salvage RT (sRT) for later than 5 weeks. Of 116 lesions, 69 lesions (59.5%) and 47 lesions (40.5%) underwent cRT and sRT, respectively. The median tumor size was larger in the cRT group (7.2 cm vs. 5.3 cm; *P*=.045). In the cRT group, the 1-year and 2-year LFFR were 94.6% and 79.5%, respectively, and in the sRT group, those were 70.6% and 50.7%, respectively (*P*=.005). In multivariate analysis, cRT independently predicts favorable LFFS (hazard ratio, 4.15; 95% confidence interval, 1.56–10.86; *P*=.004).

Conclusions: We found optimal timing of RT for incomplete TACE as within 5 weeks after TACE. Early application of RT within 5 weeks after TACE was associated with better local control.

Keywords: Radiotherapy, Transarterial chemoembolization, Hepatocellular carcinoma, BCLC stage B

OP-095

Validation of ADV Score as a Quantifiable Prognostic Biomarker for Hepatocellular Carcinoma Recurrence after Liver Transplantation

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Aims: We assessed the prognostic power of ADV score (alpha-fetoprotein-DCP-tumor volume: score (AFP (ng/ml) x DCP [PIVKA-II] (mAu/mL) x tumor volume (mL): expressed in $\log_{10}$) for predicting risk of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT). In patients with multiple tumors, total tumor volume was calculated as the volume of the largest tumor multiplied by tumor number.

Methods: This study include 668 recipients who underwent LT for HCC between 2007 and 2013 and followed up until 2018. Patients showing complete pathological response after pretransplant locoregional treatment were excluded. Tumor recurrence rate and patient survival rate were assessed according to ADV score.

Results: During follow-up, 151 patients (22.6%) showed HCC recurrence and 147 patients (22.0%) died due to HCC recurrence. Distribution of ADV scores were < 2log in 38 (5.7%), 2-3log in 115 (17.2%), 3-4log in 188 (28.1%), 4-5log in149 (22.3%), 5-6log in 85 (12.7%), 6-7log in 56 (8.4%), 7-8log in 19 (2.8%) and >8log in 18 (2.6%). Tumor recurrence rate and patient survival rate were closely correlated with ADV score (P<0.001). 5-year patient survival rate was around 85% in ADV score of 3log, 75% in ADV score of 5log, 50% in ADV score of 7log and 20% in ADV score of 8log (P<0.001). These ADV score-dependent prognostic stratification was well maintained in subgroup analyses with pretransplant locoregional treatment group and multiple tumor group (P<0.001).

Conclusions: Our results suggest that ADV score is an integrated surrogate prognostic biomarker which can be reasonably applicable to LT recipients with HCC.

Keywords: Recurrence, Tumor marker, Hepatocellular carcinoma, Biomarker

OP-096

Incidence and Risk Factors for Herpes Zoster after Adult Liver Transplantation

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Aims: Herpes zoster (HZ) is caused by reactivation of the varicella zoster virus, which occurs frequently in liver transplant recipients with impaired cellular immunity. The purpose of this study was to evaluate the incidence and risk factors for HZ after adult liver transplantation (LT).

Methods: In our institution, 993 patients underwent adult LT from January 1997 to December 2013. We retrospectively analyzed the incidence rate of HZ and risk factors for HZ after LT.

Results: Of 993 LT recipients, 101 (10.2%) were diagnosed with HZ. The incidence of HZ at 1, 3, 5, and 10 years was 6.6%, 9.1%, 10.0%, and 11.9%, respectively. Therefore, we observed that the incidence of HZ after LT was 16.3 per 1,000 personyears. Older age (≥50 years) at LT and mycophenolate mofetil (MMF) exposure were independent risk factors of HZ infection after adult LT.

Conclusions: Patients older than 50 years or with MMF exposure are considered to be at high risk for HZ. Therefore, adult liver recipients with such factors should not be given strong immunosuppression treatments.

Keywords: Herpes zoster, Liver transplantation

OP-097

Dextroplantation of Left Liver Graft in Infants

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Aims: The position of the left side liver graft is important which could lead complications of the hepatic vein (HV) and portal vein (PV) especially in small children using variants of left lateral section (vLLS) graft. The purpose of this study was to evaluate the outcome of novel technique of implantation to the right side (dextroplantation) of vLLS in infants.

Methods: From 2015 to 2016, 8 consecutive infants underwent dextroplantation using a vLLS graft (Group D). The graft was implanted to right side of the recipient after 90 degree counter clockwise rotation; graft left HV was anastomosed to IVC using the

extended right and middle HV stump, and PV was reconstructed using oblique anastomosis without angulation. Venous complications were compared to historical control group (n=17, Group C) who underwent conventional LT using a vLLS during infancy.
Results: Group D recipients were smaller than Group C (age: 5.9 vs. 6.9 months and body weight: 6.1 vs. 7.3 kg) (P<0.05). A split LT was performed in 6 recipients (75.0%) in Group D and in 7 recipients (41.2%) in Group C. In Groups D, there was no HV complication and one PV complication (12.5%). There were one HV complication (5.9%) and one PV complication (6.3%) in Group C (P>0.05).
Conclusions: Dextroplantation of vLLS graft was eligible in small recipients. Venous complications were comparable to conventional vLLS transplantation in infants. The long-term outcome should be validate.

OP-098

Effect of Everolimus on Hepatocellular Carcinoma Recurrence after Liver Transplantation

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Aims: This study was retrospectively conducted to reveal the effect of everolimus (EVR) particularly in the HCC patients who underwent liver transplantation (LT).
Methods: Total 311 HCC patients underwent LT during the study period. We divided the patients into two groups; TAC group and EVR group. TAC group maintained their TAC blood level around 5-8 ng/mL. EVR blood level was around 3-5 ng/mL with low dose TAC < 5 ng/mL. We compared the oncologic outcomes.
Results: Seventy-seven recipients (24.8%) had tumors above Milan criteria (MC) before LT. The number of EVR group was 114 (36.7%), TAC group was 197 (63.3%). More LDLTs were performed in EVR group (78.1%) than TAC group (65.0%; P=0.015). EVR group included more patients with above MC than TAC group (32.5% vs 10.3%, P=0.020). However, HCC recurrence happened more in TAC group than in EVR group (19.3% vs 9.6%, P=0.025). EVR group showed better outcomes both in recurrence-free survival and overall patient survival rates (P=0.029 and P<0.001, respectively). EVR group within MC showed better recurrence-free survival than TAC group, but there was no significant difference between two groups who had tumors beyond MC. However, in the overall patient survival rates, EVR group showed better outcomes than TAC group regardless of their tumor status. In the Cox regression analysis, EVR was an independent factor decreasing risk of HCC recurrence after LT (HR: 0.352, P=0.003).
Conclusions: EVR-based immune suppression showed better oncologic outcomes after LT for HCC patients and was an independent factor decreasing the risk of HCC recurrence.

OP-099

Minimal Invasive Living Donor Right Hepatectomy: An Experience of Consecutive 114 Cases by a Single Surgeon

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Aims: Because the donor is not performed operation under pathologic condition, it is important to consider the quality of life such as cosmetic effect. The aim of this study was to evaluate the safety and feasibility of minimal invasive living donor right hepatectomy.
Methods: All consecutive cases of minimal invasive living donor right hepatectomy between January 2014 and March 2018 in a tertiary referral hospital were enrolled in this retrospective cohort study. All surgical procedures were performed by one surgeon. All patients underwent subcostal incision and incision length was applied flexibly according to the weight of the graft (9-12 cm). The group was analysed in terms of donor demographics, preoperative data, postoperative outcomes.
Results: The mean age of the donors was 27.4 ± 6.7 years, the gender ratio for men and women was 18:96. The mean operative time was 402.5 ± 78.8 minutes and mean postoperative hospital stay was 10.1 ± 1.7 days. The number of complications was 6 cases (5.3%) and among them, the Clavien-Dindo classification III or higher complication was 2 (1.8%). There were no mortality cases.
Conclusions: Minimal invasive living donor right hepatectomy was a safe and feasible procedure for donors. It showed an acceptable incidence of complications. The authors suggest that minimal invasive living donor right hepatectomy could be a reasonable operative option for donors in terms of cosmetic effect.

OP-100

The Protective Effect of Antioxidants against Hepatic Ischemia Reperfusion Injury in Rat

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Aims: Hepatic ischemia reperfusion (I/R) injury is a major complication of liver surgery, including hepatic surgery, liver transplantation, and trauma. Antioxidants including citric acid, cassia tora and hesperidin reduces oxidative stress and inflammation during hypoxia and reoxygenation. Our objective was to investigate the protective effect of antioxidants against hepatic I/R injury in rat.
Methods: We fed Sprague-Dawley rats citric acid, cassia tora

and hesperidin (100 mg/kg/d). One week later, ischemia was induced by clamping the common hepatic artery and portal vein of rats for 30 minutes. Rats were randomized to three major groups that were treated as follows: (1) the sham operated group; (2) the I/R group; (3) the I/R-antioxidants group. Albumin, bilirubin, AST, ALT, nitric oxide, superoxide dismutase, catalase, glutathione peroxidase and antioxidant were measured.

Results: Compared with the sham group, the I/R group had higher expression of AST and ALT and lower expression of catalase, superoxide dismutase, glutathione peroxidase, antioxidant, nitric oxide and albumin. Compared with the I/R group, the I/R-antioxidant group had higher expression of catalase, superoxide dismutase, antioxidant and nitric oxide and lower expression of AST and ALT.

Conclusions: These results suggest that antioxidant therapy has a significant therapeutic potential in ischemic liver injury.

Keywords: Antioxidant, Ischemia reperfusion injury, Rat

OP-101

Factors Predicting Cholestasis in Post Right Lobe Donor Hepatectomy in the Era of Standardized Donor Selection Protocols: Analysis of 340 Donors over 19 Months

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Aims: Despite over 10000 LDLTs completed worldwide the Right lobe donation continues to carry high risk donation status. Of all the reported donor mortalities post-operative liver failure secondary to small remnant is still the highest. Hence we analyzed the factors which leads to post donor hepatectomy cholestasis (PDHC).

Methods: Retrospective analysis of 340 donors during the time period of 06-02-2017 to 12-09-2018 was done. Our group has experience of 2800 LDLTs with zero donor mortality.Data analysis was done based on two cut off values of Total bilirubin (TB) one based on the median of Peak bilirubin(PB) of the study cohort and another based on 5 mg % which is universally accepted as the cut off for defining post-operative liver failure and small for size syndrome.

Results: On analysis 2.3 mg % was found to be the median PB. With 2.3 mg% cut off Day -1 TB, Day-5 TB, POD to normal TB, Peak INR, % of liver remnant were statistically significant @ $P<0.05$. On analysis with 5.0 mg % cut off Male gender, BMI, Blood Group-O, Area of middle hepatic vein congestion, Day -3 INR, peak INR, Day -1 TB, Day-5 TB, POD to Normal TB and Hospital Stay were statistically significant @ $P<0.05$.

Conclusions: High risk for PDHC includes Males, High BMI, Blood Group "O" and high middle hepatic vein congestion area. Peak INR and POD -3 INR were significantly higher in this group. They tend to have significantly higher TB on POD-1, POD-3 and PB along with prolonged hospital stay.

OP-102

Oncologic Outcome of Two Stage Hepatectomy in Patients with Bilobar Multiple Colorectal Liver Metastases

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Aims: Two stage hepatectomy has been widely performed for last decades as the paradigm of definition of resectability has shifted. There are many studies that advocate the efficacy of two stage hepatectomy, but rare reports that pactically compare the oncologic outcome between surgical group and non-surgical group.

Methods: From January 2010 to November 2018, 51 patients were planned for 2 stage hepatectomy and 43 patients were enrolled for this study. One of three modalities were used for 2 stage hepatectomy (Portal vein embolization (PVE), Selective ligation of Portal vein (PVL), ALPPS). Control group was selected according to the criteria below; Before 2010, when two stage hepatectomy has started in our institution, patients who were received R0 resection of colon cancer diagnosed colorectal cancer with bilobar multiple liver metastases and without other organ metastasis.

Results: PVE, Selective ligation of PV, ALPPS were performed in 12 (27.9%), 17 (39.5%), 13 (30.2%) cases. Postoperative motility occurred in 2 patients (4.7%). Recurrence was observed in 29 patients (67.4%) and among them, 19 patients (44.2%) showed early recurrence within 6 months. 7 patients (16.3%) were alive without disease, and 15 patients (34.9%) were alive with disease. In terms of overall survival, 2 stage hepatectomy group showed statistically significant prolonged survival ($P<0.001$) with 36% of 5 years survival.

Conclusions: Two stage hepatectomy can give better oncologic outcome compared to non-surgically treated group in patients with colorectal bilobar multiple liver metastasis. Therefore aggressive surgery is worthwhile and challengeable despite of technical difficulty.

OP-103

Surgical Tips of Pure Laparoscopic Donor Right Hemihepatectomy for Donors with Portal Vein Anatomical Variations

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Aims: Several reports from centers highly specialized in living-donor liver transplantation and laparoscopic liver surgery addressed good outcomes of total laparoscopic living donor hepatectomy for adults. However, donors with anatomical variations of the right portal vein or hepatic ducts or with marginal liver grafts are considered unsuitable for this procedure by most centers.

Methods: From March 2017 to November 2018, 15 cases of pure laparoscopic right hemihepatectomy in a donor with portal vein variation were performed by the single experienced surgeon. We describe in this report about the standardized procedure for safe totally laparoscopic adult living donor hepatectomy for donors with variations of the right portal vein.

Results: Right hepatic artery should be temporary clamped for making demarcation line. We usually do not dissect around artery for preventing hidden injury of the hepatic artery. Instead, we clamped right side of Glissonian tissue bluntly after isolating right portal vein. Bile duct division was performed using ICG cholangiography. We usually used bulldog clamp during the first bile duct division for preventing bile spillage that disturbing ICG cholangiography during the division of the other bile duct. There are different methods to control the right portal vein branches including 1) Hem-o-lock clips supported with metal clips. 2) Laparoscopic vascular staplers. 3) Hem-o-lock clips to temporary control the portal vein branches stumps which are then replaced with sutures (continuous prolene 5/0 sutures). Then hem-o-lock clips could be removed from the portal vein stumps.

Conclusions: Portal vein anatomic variations can be overcome by appropriate surgical procedures.

OP-104

Subtotal Hepatectomy: Pig Models for the Study of Post-Hepatectomy Liver Failure

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Aims: Partial hepatectomy (PHx) in the rat can be easily performed and reproducible; however, the physiology and anatomy of the rat is not strictly comparable to those of human. Therefore, to understand better the pathophysiology of post-hepatectomy liver failure (PHLF) in human, it is necessary to establish a standardized hepatic failure model in large animals, which closely correlates to clinical setting and can be reproduced. The aim of this study was to develop a pig model of PHLF that could accurately reproduce the liver failure parameters of the corresponding clinical syndrome that may develop after extensive liver resections.

Methods: Thirteen pigs were divided into 3 groups; sham operation group (n=3), 70% hepatectomy group (n=5), 90% hepatectomy group (n=5). 10 pigs except sham operation underwent 70% and 90% hepatectomy. In 70%-hepatectomy, the left lateral and median lobes were removed, and in 90% hepatectomy, all lobes except the caudate were resected. Blood samples were collected before the operation, 1, 6 hours and at regular intervals (every 8h) for measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL) and prothrombin time (PT). Animals were sacrificed 48 hours after hepatectomy was completed.

Results: In a 70% PHx group showed restoration of liver injury (AST, ALT) and liver function (TBIL, PT) parameters within 48 hours. However, in a 90% PHx group, TBIL was elevated after hepatectomy and increased until 48hours. Furthermore, unlike 70% PHx group, TBIL was not recovered. These results indicated that the 90% PHx model was closer to the PHLF model than 70% PHx model.

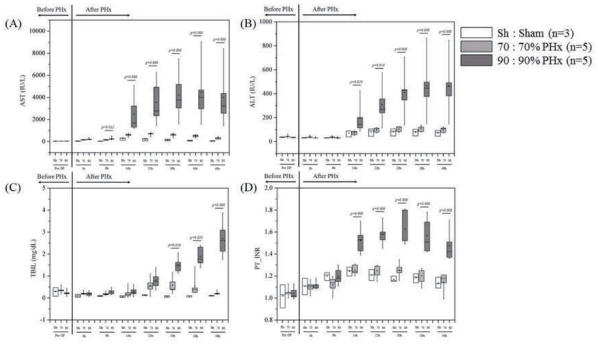

Fig.1. Pre- and postoperative evaluations of AST (A), ALT (B), total bilirubin (C), and prothrombin time (D) among sham, 70% PHx, and 90% PHx group.
Data are expressed as median, with the 25%–75% percentiles in boxes and the 55–95% percentiles as whiskers.

Conclusions: We established various models of partial hepatectomy in pig for development of the reproducible model of PHLF. The result suggests that 70% hepatectomy does not represent the clinical picture of PHLF.

Keywords: Partial hepatectomy, Post-hepatectomy liver failure, Animal model

OP-105

Choice the Optimal Surgical Treatment Strategy for Liver Alveococcosis

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Aims: Development classification of liver alveococcosis, based on modern approaches to treatment to ensure radical treatment. Those classification should determine treatment tactics, routing admission of patients, evalution and comprasion of results.

Methods: The criteria which were used in classification: 1. The

volume of liver damage; 2. Invasions of afferent and efferent vascular structures; 3. Involvement of neighboring organs; 4. The presence of regional and distant metastases and their resectable; 5. The volume of future liver remnant with measuring of fibrosis of its parenchyma.

Results: Patients were diveded 4 groups: resectable, borderline-resectable, unresectable, incurable. To each group of patients is determined optimal treatment: Resectable - standart resection without stimulation of hypertrophy (performed in any HPB-center), Borderline-resectable - Classical resection, resection with total vessels isolation of remnant and its conservation. in situ, ex situ, thermal, cold, autotransplantation with resection of the main vessels, Unresectable – any volume of liver damage with its fibrosis, resectable distant metastases. Orthotopic liver transplantation (full size/living donor), Incurable – symptomatic, palliative care. From 2008 to 2019 in «Volga district medical center» were treated 71 patients with liver alveococcosis. By groups: resectable (n = 16), borderline-resectable (n = 36), unresectable (n = 13), incurable (n = 6). 58 patients radical operated: 52 – R0 resection,5 – full size OLT+ 1 partial liver transplantation from living donor. In group of R0 resections 62% were extented liver resections (>4 segments), resection and reconstruction of the main vessels were in 47% (IVC in 28 cases, PV in 24 cases) In 34 cases was perfomed resection and reconstructions of extrahepatic bile ducts, in 33% was perfomed resection of such neighboring organs as diaphragm, lung, right adrenal, duodenum, stomach, colon. In 5 cases were "ex vivo" resection followed by autotransplantation, in 3 cases with a reverse autotransplantation of the left lateral sector. The incidence of PHLF degree A and B (ISGLS) did not exceed 10%. Complications (Clavien-Dindo) in 32 cases: grade II-8, IIIb-15, IVb -2, V-7. Bileleakage (ISGLS): class B -7, class C-13. All patients treated with obligate adjuvant antiparasitic therapy.

Conclusions: The new classification of liver alveoccosis is clinically acceptable and can be recommended for use.

Keywords: Liver alveococcosis, Liver resrction, Liver transplantation, Classification

OP-106

Robotic Hilar Cholangiocarcinoma Radical Resection Compared with Laparotomy in Prognosis

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Aims: Performing robotic resection for the treatment of hilar cholangiocarcinoma (HCC) is not universally accepted as an alternative approach to open surgery, and only a limited number of such procedures have been reported due to the difficulty of radical resection and the lack of consensus regarding the adequacy of this approach. We aimed to describe our experience with robotic HCC radical resection with long-term outcome and to compared its short-term outcome with those of open HCC radical resection in HCC patients.

Methods: We retrospective reviewed medical records of 45 patients who underwent robotic approach and open approach between January 1st 2016 and December 31st 2016 at the department of HPB oncology surgery in Chinese PLA general hospital. All cases were confirmed by pathology histological.

Results: The retrospective study contains 15 females and 30 males, with mean age was 62.5±9.3. R0 rate was 71.1%. With 23 months follow-up, there was no significant difference in overall survival between two group and 1-year overall survival rate was 57%. Also, there was no statistically significant different in tumor size, resection margin, 30-days mortality and short-term complication including DGE, massive hemorrhage and surgical related infection between two group. However, the robotic resection group show longer operating time, less estimated intraoperative blood loss, less fasting days, shorter hospital stay and higher total costs.

Conclusions: Compared with laparotomy, robotic HCC radical resection could concluded as an equivalence or non-inferiority approach with acceptable long-term outcome.

OP-107

Robotic Anatomical Hepatectomies for Difficult Segments

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Aims: Central bisectionectomy, anterior sectionectomy, and posterior sectionectomy are technically demanding procedures in minimally invasive approach because of difficult expoure and extensive parenchymal transection planes. With limited robotic instruments including absence of CUSA, these procedures have been rarely perfomed by robotic approach.

Methods: Consecutive robotic central bisectionectomy, anterior sectionectomy, and posterior sectionectomy were performed. Patients were all males and were 67, 71, and 41-years-old, respectively. Pathologic diagnoses were all hepatocellular carcinomas of each 4.4, 4.2, and 3.2 cm diameter. Operative settings were identical for the three kinds of procedure. The patients were placed in supine with a reverse Trendelenburg and right side elevation. Umbilical 12-mm camera port, three 8-mm ports and additional 12-mm assistant port were used. Glissonian approach and ICG fluorescence image clearly demarcated the resection planes. Parenchymal transection was performed using the Maryland bipolar dissector and harmonic scalpel. The rubber band self-retraction method and third arm of robot system helped for stable and excellent exposure of surgical planes. All procedures were similar. Here, we present robotic central bisectionectomy.

Results: There were no conversions to laparoscopic or open surgery. The operative time was 320, 330, and 290 min and estimated intraoperative blood loss was 200, 330, and 250 ml. The pathologic surgical margin was 2.5, 0.5, and 3.6 cm.

The length of stay after surgery was 7, 8, and 6 days and there were no postoperative complications.

Conclusions: Robotic central bisectionectomy, anterior sectionectomy, and posterior sectionectomy are still demanding procedures with long operative time. However, these procedures could be performed safely in regard to short-term perioperative outcomes. Robot surgical system provided several benefits for anatomical hepatectomies including a stable and excellent operative field and clear surgical planes.

Keywords: Robot, Hepatectomy, Hepatocellular carcinoma

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Poster Exhibition

Alcoholic Liver Disease

PE-001

Randomized Controlled Trial of Lactulose and Lactulose with Probiotic in the Treatment of Minimal Hepatic Encephalopathy in Chronic Liver Disease

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Background: Minimal Hepatic Encephalopathy (MHE) has impact on future clinical outcomes, such as occurrence of overt hepatic encephalopathy, quality of life and survival. This study is conducted to compare lactulose and lactulose with probiotic in treatment of MHE in chronic liver disease.

Methods: In this stratified randomized controlled trial 62 patients were stratified according to Child Turcott Pugh (CTP) Score into three blocks (Child's A, B and C) and each block randomized into two groups (lactulose alone and lactulose with probiotic). The primary end point was to evaluate cognitive status after 1 month as assessed with Figure Connection Test (FCT) A and B scores in comparison to the baseline. The secondary end points were to estimate the prevalence of MHE in chronic liver disease and assess association of MHE and inflammatory markers.

Results: 90% of Child's A showed improvement in FCT A and B in both groups. Lactulose improved FCT A and B in 45.45% and 40% while lactulose with probiotic improved FCT A and B in 54.54% and 30% in Child's B and C respectively. Those with higher baseline values had significantly lesser degree of improvement in FCT A and FCT B values among all groups. Total leukocyte count (TLC) was also significantly higher in those who didn't improved among all groups, (6584.21 vs. 9100, *P* value 0.058; 5198.18 vs. 8318.18, *P* value 0.00; 5157.14 vs. 10143.08, *P* value 0.00 respectively). The prevalence of MHE was found to be 41.33%.

Conclusions: There was no difference in cognitive status between lactulose alone and combination of lactulose and probiotic. Improvement in FCT A and B scores was significantly affected by baseline FCT A and B scores and TLC.

Keywords: Minimal hepatic encephalopathy (MHE), Child turcott pugh (CTP) score, Figure connection test (FCT) A and B

PE-002

Peptic Ulcer Disease in Cirrhosis

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Introduction: Peptic ulcer bleed (PUB) is associated with increased mortality in both compensated and decompensated cirrhosis. Knowing the frequency of Peptic Ulcer Disease (PUD) and accurate documentation of bleeding source will avoid inappropriate therapeutic procedure in patients with cirrhosis and gastrointestinal bleeding while missing the diagnosis results in fatal outcome. This study is conducted to describe the prevalence of PUD in cirrhosis.

Methods: This is a retrospective study that included 199 patients with chronic liver disease (CLD) referred to upper gastrointestinal (UGI) endoscopy during last 6 months. The primary end point was to describe prevalence of PUD among these patients. The secondary end point was to evaluate the association between PUD, child's class and portal hypertensive gastropathy (PHG).

Results: The prevalence of PUD in patients with cirrhosis was 32.1% and its prevalence according to Child Pugh A, B and C was 18.8, 42.2 and 39.1% respectively. The occurrence of PUD with respect to presence and absence of PHG is 34.2 and 26% respectively.

Conclusions: There is high prevalence of PUD in CLD. However, there is no statistically significant correlation between PUD, Child's class and PHG.

Keywords: Chronic liver disease (CLD), Peptic ulcer bleed (PUB), Portal hypertensive gastropathy (PHG)

PE-003

Beneficial Effects of Cisplatin on Liver Fibrosis in a Non-Alcoholic Steatohepatitis (NASH) Rodent Model

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Aims: Liver fibrosis occurring as an outcome of non-alcoholic steatohepatitis (NASH) can precede the development of cirrhosis. We investigated the effects of cisplatin in preventing liver fibrosis in a rodent model of NASH.

Methods: Adult Sprague-Dawley rats were fed a choline-deficient high-fat diet and exposed to diethylnitrosamine for 6 weeks. The NASH group (n = 10) received vehicle and the cisplatin group (n = 10) received 2.5 mg·kg(-1)·day(-1) by gavage. A control group (n = 4) received only standard diet and vehicle. Following treatment, animals were sacrificed and liver tissue was collected for histologic examination, mRNA isolation, and analysis of mitochondrial function. Genes related to fibrosis (MMP9, TIMP1, TIMP2), oxidative stress (HSP60, HSP90, GST), and mitochondrial biogenesis (PGC1α) were evaluated by real-time quantitative polymerase chain reaction (RT-qPCR). Liver mitochondrial oxidation activity was measured by a polarographic method, and cytokines by enzyme-linked immunosorbent assay (ELISA).

Results: Cisplatin treatment restored mitochondrial function and reduced collagen deposition by nearly 63% compared to

the NASH group. Cisplatin upregulated PGC1α and MMP9 and reduced TIMP1 and TIMP2 mRNA and IL-6 and IL-10 protein expression. There were no differences in HSP60, HSP90 and GST expression.

Conclusions: Cisplatin modulated PGC1α expression, improved mitochondrial respiration and prevented collagen deposition. It may, therefore, be useful in the treatment of liver fibrosis in NASH.

Keywords: Liver fibrosis, Non-alcoholic steatohepatitis, Cisplatin, Mitochondrial respiration

PE-004

Preclinical and Clinical Study in Alcohol Dependence Syndrome Patients with Lipid Profile and Cardiac Markers to Correlate Occurrence of Cardiovascular Disease

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Aims: The Objective of this study was to correlate the Lipid Profile and cardiac markers along with cardiovascular Risk in Alcohol dependence syndrome patients.

Methods: This is a hospital based cross sectional study conducted in ASUNTA Medicare Hospital Pvt. Ltd., Bhaktapur, Nepal. The Study population comprises of 90 case and 90 control as a participant. Patients fulfilling the criteria of search work were included after taking informed consent the test was performed by reagent manufactured by Human, Germany in the fully automated chemistry Analyzer, BT, 3000, Italy. Performa were prepared for the measurement of sociodemographic variables and questinnaire done for the participants statistical analysis was done by using SPSS-20.

Results: Mean ages of cases and controls were 32.12 ± 6.35 and 33.29 ± 5.12 Respectively. Most of the participants in the case were smokers (85%) chewing tobacco (60%) comparison of mean of SGOT in case (35.26 ± 14.27) and control (114.35±46.22) was found Statistically significant. $P < 0.001$ the mean total cholesterol levels were found to be higher in case (6.05±0.85) than control (4.56 ± 0.12) with a positive statistically significance ($P < 0.001$). Likewise mean triglyceride along with HDL-cholesterol and LDL-cholesterol were also high in case compared with control, $P < 0.001$. Myoglobin was found to be higher in chronic Alcoholic patients.

Conclusions: Alcohol Dependence Syndrome is a challenging worldwide problem which leads to premature death. Liver dieses and cardiovascular risk prolonged use of Alcohol leads to structural and Functional damage of Heart which can be easily monitored under echocardiography along with Variation in cardiac function test. Study Shows that the patient needs regular blood test to prevent the cardiovascular risk liver disease and others Physiological abnormalities. Early identification of excessive alcohol consumption and alcoholism could improve the possibility of early treatment cost. This Study shows that alcoholic patient should be monitored for lipid profile as there is risk for cardiovascular disease.

PE-005

Unexpected Improvement of Liver Function by Intravenous Immunoglobulin in a Steroid-Experienced Severe Alcoholic Hepatitis

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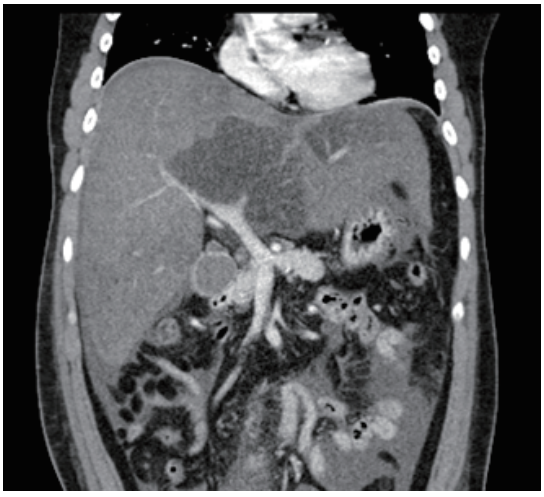
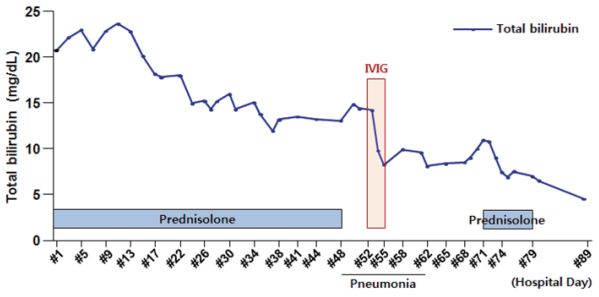
Aims: Corticosteroid is the treatment of choice for severe alcoholic hepatitis; however, it can also lead to severe life-threatening infection. In this study, we report a severe alcoholic hepatitis patient who did not achieve a satisfactory improvement of the liver function by corticosteroid use but obtain a significant improvement of the liver function by intravenous immunoglobulin (IVIG).





Methods: A 28-year-old man visited the emergency department with the chief complaint of jaundice and abdominal discomfort. The initial clinical presentations, laboratory test results, and radiologic imaging led to the diagnosis of severe alcoholic hepatitis. This patient was initially treated with corticosteroids. Later, he developed pneumocystis pneumonia. To control the

infection after a prolonged corticosteroid usage, IVIG was administered. IVIG was administered according to the protocol used in sepsis (500 mg/kg daily for 3 days).
Results: The patient successfully recovered from the infection after administrating antibiotics and IVIG. IVIG led to an unexpected remarkable decrease in the serum total bilirubin level and restored the responsiveness to the additional corticosteroid used after the resolution of the infection.
Conclusions: IVIG is widely used to control systemic inflammation. Its immunosuppressive property may also have a beneficial effect in severe alcoholic hepatitis patients. Furthermore, IVIG's immunomodulatory activities may work by increasing the number of corticosteroid receptors in steroid-resistant states, causing improved steroid responsiveness in SAH. IVIG may be a possible candidate for the second-line treatment of severe alcoholic hepatitis.
Keywords: Alcoholic hepatitis, Intravenous immunoglobulin, Corticosteroid

PE-006

A Case of Pneumocystis Pneumonia after Use of Glucocorticoids in Severe Alcoholic Hepatitis

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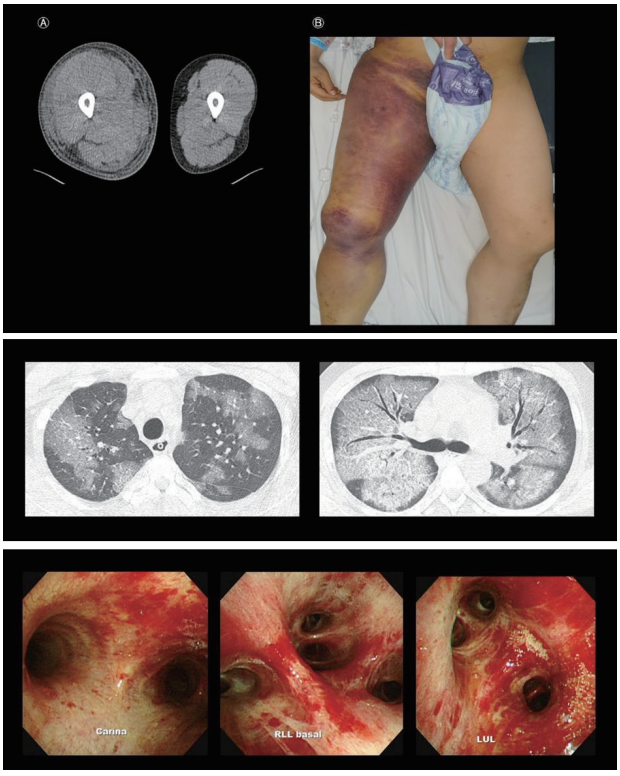
Aims: Severe alcoholic hepatitis (AH) is a lethal disease (3-month mortality: ~50%) that has a clinical syndrome of jaundice with other signs of liver decompensation in alcohol abusers.
Methods: The most current guideline recommends glucocorticoids as first-line agents in patients with severe AH to reduce short-term mortality. However, diverse and significant toxicities of systemic glucocorticoids often occur. Especially, infection, which is one of the complications from steroid use, can result in serious outcomes, such as acute-on-chronic liver failure, in patients with severe AH.
Results: Pneumocystis pneumonia (PCP) is a life-threatening opportunistic infection for which 20 mg of prednisone is prescribed for more than one month. Therefore, when glucocorticoids are used at a certain dose or over a certain period, prevention of PCP is warranted. Although trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for the prophylaxis of PCP, its hepatotoxicity prevents its frequent use in patients with severe AH who are on high-dose glucocorticoids. Moreover, there is no definite consensus on prevention of PCP in severe AH patients on steroid treatment.
Conclusions: Herein, we report a case of a 43-year-old male with PCP resulting in death after use of glucocorticoids for severe AH. To date, prevention of PCP in severe AH patients on corticosteroids treatment has been overlooked, and this case emphasizes the need for prophylaxis of PCP in severe AH patients on corticosteroids.



Keywords: Hepatitis, Alcoholic, Glucocorticoids, Pneumonia, Pneumocystis, Trimethoprim, Sulfamethoxazole drug combination

PE-007

CX3CR1-Mediated Differentiation of F4/80low Monocytes into F4/80high Kupffer-Like Cells in Alcoholic Liver Disease

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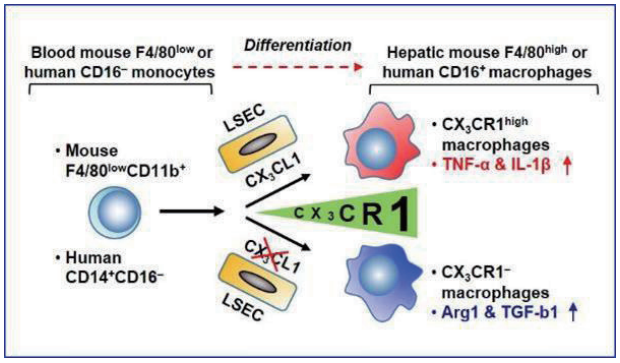
Aims: Kupffer cells play key roles in progression of alcoholic liver disease as well as modulation of liver immune homeostasis. Kupffer cells are known to be originated from yolk sac and bone marrow, but the exact mechanism of differentiation of bone marrow derived monocytes (BMmos) into Kupffer cells has not been clearly elucidated. CX_3CR1-CX_3CL1 axis is involved in migration and signaling in monocyte-macrophage lineage cells. In present study, we investigated CX_3CR1 dependent differentiation of BMmos into Kupffer cells and identified how bone marrow derived Kupffer cells function in alcoholic liver disease.
Methods: Mouse and human monocytes were cultured with CX_3CL1 expressing liver sinusoidal endothelial cells (LSECs) and human umbilical vein endothelial cells (HUVECs). HUVECs were treated with siRNA for silencing CX_3CL1. Kupffer cells were de-

pleted by clodronate and $CX_3CR1^{+/GFP}$ bone marrow cells were adoptively transferred to $CX_3CR1^{+/+}$ mice. To induce alcoholic liver injury, mice were fed with 4% ethanol liquid diet for 8 weeks.
Results: Mouse $CX_3CR1^{low}F4/80^{low}$ monocytes and human $CX_3CR1^{low}CD16-$ monocytes were differentiated into $CX_3CR1^{high}F4/80^{high}$ or $CX_3CR1^{high}CD16^{+}$ macrophages by co-culture with LSECs and HUVECs. CX_3CL1 deficiency in HUVECs attenuated the expression of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), whereas CX_3CL1 treatment reversed this expression in co-cultured BMmos. After Kupffer cell depletion, differentiation of BMmos into Kupffer cells in CX_3CR1 null mice ($CX_3CR1^{GFP/GFP}$) were reduced compared to $CX_3CR1^{+/GFP}$ mice. Bone marrow derived Kupffer cells ($CX_3CR1^{+}F4/80^{high}$) showed higher expression of IL-1β and TNF-α than $CX_3CR1^{-}F4/80^{high}$ Kupffer cells. In alcoholic liver disease model, $CX_3CR1^{GFP/GFP}$ mice showed less liver injury, hepatic fat accumulation, and inflammatory responses than $CX_3CR1^{+/GFP}$ mice.



Conclusions: CX_3CR1 plays critical roles in differentiation of BMmos into Kupffer cells and pro-inflammatory functional conversion of bone marrow derived Kupffer cells. CX_3CR1 could be a marker to identify Kupffer cell subsets and might be a novel therapeutic target in alcoholic liver disease.
Keywords: CX3CR1, CX3CL1, Monocyte, Kupffer cell, Alcoholic liver disease, Liver sinusoidal endothelial cell

PE-008

Essential Amino Acid Supplementation Decreases Liver Damage Induced by Chronic Ethanol Consumption in Rats

Bauyrzhan DARZHIGENOV, Darkhan KOPZHASSARULY

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Aims: The liver sustains the greatest damage from ethanol (EtOH) abuse. EtOH and its metabolites impair hepatocyte metabolism, causing intracellular accumulation of proteins and lipids and increasing radical oxygen species production. These processes are toxic to the mitochondrial respiratory chain and to mitochondrial DNA. It has recently shown that supplementating the diet of rodents with an essential amino acid-enriched mixture (EAAem) significantly increases mitochondrial mass and number in cardiac and skeletal muscles and improves mitochondrial function in aged animals.
Methods: Thus, in this study we sought to test whether EAAem supplementation could reduce EtOH-induced liver damage. Groups of adult male Wistar rats were fed a standard diet and water ad libitum (the control group), drinking water with 20 percent EtOH (the EtOH group), or drinking water with 20 percent EtOH and EAAem supplementation (1.5 g/kg/day) (the EtOH+EAAem group) for 2 months. The blood EtOH concentration was measured, and markers for fat (Oil-Red-O), mitochondria (Grp75, Cyt-c-ox), endoplasmic reticulum (Grp78), and inflammation (Heme Oxigenase 1, iNOS, and peroxisomes) were analyzed in the liver of animals in the various experimental groups.
Results: EAAem supplementation in EtOH-drinking rats ameliorated EtOH-induced changes in liver structure by limiting steatosis, recruiting more mitochondria and peroxisomes mainly to perivenous hepatocytes, stimulating or restoring antioxidant markers, limiting the expression of inflammatory processes, and reducing ER stress.
Conclusions: Taken together, these results suggest that EAAem supplementation may represent a promising strategy to prevent and treat EtOH-induced liver damage.
Keywords: Ethanol, Mitochondrial respiratory, Mitochondrial DNA, Steatosis

PE-009

Types and Pattern of Alcoholic Drinks Consumption and the Knowledge of Liver Cirrhosis and Alcohol Related Health Hazards among Selected Nepalese People

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Aims: Alcoholic liver disease and more specifically cirrhosis is one of the most common and serious conditions caused by alcohol consumption. This study is conducted with the objectives of determination of the type and pattern of use of alcoholic drinks and the knowledge of the health effects of alcohol, particularly the liver cirrhosis in Nepalese people.
Methods: This is a cross sectional observational study conducted among 210 adult Nepalese people. A structured pretested questionnaire was used as a tool of the study. It includes the demographic information of the respondents, information about the type and frequency of alcoholic drinks taken along with the various health hazards of alcohol, with the knowledge of liver cirrhosis as a separate question. Consent was taken prior to enrolling the participants in the study. Chi square test was used to note the differences in groups with P value of <0.05 as significant.
Results: Among a total of 210 respondents, 138 (65.7%) were males and 72 (34.3%) females. The mean age was 31.68 years with standard deviation of 7.21 and range 21 to 57 years. A total of 156 (74.3%) had consumed alcohol once in their lifetime and 54 (25.7%) were previous drinkers. Beer (102, 48.6%) and

wine (54, 25.7%) were the common alcoholic drinks consumed. Alcohol affecting the liver as a health hazard was responded by 162 (77.1%) of the respondents. We had asked whether the participants know alcohol causes liver cirrhosis where 120 (57.1%) responded that they did. The knowledge varied significantly with the level of education (*P* value <0.001).

Conclusions: Alcohol consumption is common and beer is mostly used. Most of the participants are knowledgeable about the health risks of alcohol and just more than half knew liver cirrhosis is caused by alcohol. Continuous awareness should be done to minimize the health damage caused by alcohol.

Keywords: Alcohol, Alcoholic liver disease, Liver cirrhosis, Knowledge

PE-010

Study of Biochemical and Haematological Parameters of Alcoholic Liver Disease Patients

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Aims: Alcoholic liver disease is one of the leading cause of morbidity and mortality all over the world. Liver disease reduces the functioning of the liver. Hence the study was designed to evaluate the status of biochemical markers in alcoholic liver disease among Nepalese population.

Methods: This study was carried out in the department of biochemistry Kaski Sewa Hospital and Research Center & Manipal Teaching Hospital, Pokhara, Nepal between Feb 15, 2018 to march 5, 2019. Clinically diagnosed 60 alcoholic liver disease patients and 60 healthy non alcoholic controls were enrolled for the study. Liver function test panel and Haematological parameters (Hb, RBC, MCV and platelets) were determined for all the subjects. The comparision between the two groups were evaluated by pearson correlation coefficient. Statistical analysis were performed by by using SPSS version 17.0. A *P* value of < 0.05 was considered statistically significant.

Table 1. Comparision of variables between ALD and Healthy controls.

Parameter	ALD Subjects (n=60) Mean±SD	Control (n+55) Mean±SD	P value
Age	49.52± 16.27	47.05± 17.94	0.003
Total Protein	7.51± 1.02	7.65± 0.61	0.000
Albumin	3.77± 0.59	4.09± 0.41	0.000
Total Billirubin	1.38±1.43	0.70±0.35	< 0.001
Direct Billirubin	0.59±0.81	0.26±0.11	< 0.001
AST	127.25± 151.73	23.47±8.20	0.000
ALT	70.58±63.23	22.32±6.12	0.000
AST/ALT ratio	1.86±1.30	1.09± 0.37	0.000
ALP	124.43± 60.30	84.50± 30.53	0.000
Gamma GT	130.82± 75.39	26.44± 10.68	0.000

A P value <0.005 is considered statistically significant.

Results: A total of 110 participants were included in this study. out of which 79 were males and 31 were females. The mean age of the study subjects was 48.34 ± 17.06. All the results were expressed as mean ± SD. This study found a significant difference between alcoholic liver disease patients and nonalcoholic healthy controls. The mean value of AST and ALT was found to be statistically significant (*P* < 0.001). The mean value of AST was increased more than that of ALT. We also found a higher AST/ALT ratio (1.86±1.30) in alcoholic liver disease in comparision to healthy controls which is statistically significant (*P* < 0.000).Enzyme levels of GGT and ALP is elevated in ALD (*P* < 0.000). A high Mean corpuscular volume (MCV) is observed in alcoholic liver disease subjects.

Conclusions: This study suggests that liver enzymes would be the best marker for alcoholic liver disease. Our study indicates that monitoring of liver enzymes in combination is a sensitive marker for diagnosing alcohol induced liver injury.

Keywords: Alcoholic liver disease, MCV, Aminotransferase, ALT

PE-011

Alchoholic Hepatitis Inital Recovery Is Complicated by Second Hit Drug Induced Liver Injury by Ayurvedic Medicines in India and Is Associated with Bad Prognosis

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Aims: Alchoholic hepatitis is a dangerous condition with high mortality.However in many part of India people take Ayurveda or homeopathic drugs to treat this condition and subsequently drug induced liver injury make the prognosis worse in most of the patients.

Methods: We follow standard guidelines in management of alchoholic hepatitis. Need for steroid is decided on the bases of maddrey score and need for transplant is decided on bases of day 7 lilly score.

Results: We describe outcomes of 13 patients who have taken Ayurveda or homeopathic drugs during the first 30 days of alchoholic hepatitis. 8 patient had initial maddrey score of less than 32. 6 out of 8 patient both maddrey and liver function was worsened who has taken these drugs during recovery. All 6 had completed transplant criteria. One patient underwent LDLT and expired post operatively.4 out of other 5 expired due to non-availability of cadaver or live donor. 1 patient recovered. 5 patients were having initial maddrey score > 32 and started on steroids. One patient had lilly score was more than 0.45 taken Ayurveda/homeopathic drugs and expired. 4 patients was having lilly score less than 45. All 4 patients deteriorated after taking Ayurveda/homeopathic drug, one patient underwent successful liver transplant. Explant pathologies showed typical features of drug induced liver injuries. 2 patient expired and one patient recovered after stopping the Ayurveda/homeopathic drugs. In both the groups, Ayurveda and homeopathic drugs were associated significantly with mortality (*P* < 0.001).

Conclusions: Ayurveda/homeopathic drugs are associated with worse prognosis in alchoholic hepatitis.

PE-012

Prevalence and Distribution of Hepatitis and Liver Cirrhosis among Elderly: Evidence from the 2017 National Survey of Older Koreans

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Aims: Alcohol consumption has increased in Korea along with the country's rapid socioeconomic development and has caused increase in the alcohol related mortality and morbidity. The study aimed to assess the prevalence of hepatitis and liver cirrhosis; and its association with socio-demographic factors among elderly population using data from the 2017 National Survey of Older Koreans.

Methods: A cross-sectional study was conducted using secondary data from the 2017 National Survey of Older Koreans. A total of 10299 elderly people aged 65 years and above were included in the study. Prevalence of hepatitis and liver cirrhosis was based on the doctors' diagnosis, and were suffering for more than three months. Descriptive statistics was used to determine the prevalence of hepatitis and liver cirrhosis, and chi-square test was applied at a 5% significance level to assess the association with socio-demographic factors.

Results: Prevalence of hepatitis among elderly people aged 65 years and above was 0.8% in Korea. There was no significant difference in the prevalence of hepatitis in regard to sex, educational level, marital status, type of residence and employment status. However, prevalence of hepatitis was significantly different among age groups, it was 1.1% in the elderly aged 65- to 69 years and 0.4% among those who were 80 years and above ($P < 0.05$). Prevalence of liver cirrhosis was 0.5%, including 0.6% among males and 0.4% among females; and 0.7% in the age group of 65-69 years and 0.1% in the age group of 80 years and above. Prevalence of liver cirrhosis did not differ across sex, educational level, type of residence and employment status. However, age group and marital status were significantly associated with the prevalence of liver cirrhosis ($P < 0.05$). Separated or divorce or single respondents had 1.1% prevalence of liver cirrhosis where as it was 0.5% among married ($P < 0.05$). Only two respondents had both diseases.

Conclusions: Prevalence of hepatitis and liver cirrhosis based on the doctor's diagnosis was relatively high among older Koreans. Both sexes were equally affected. Age was significantly associated with both hepatitis and liver cirrhosis. There is need to strengthen preventive measures in the early stage of life to reduce its burden.

Keywords: Hepatitis, Liver cirrhosis, Elderly, Korea

Autoimmune Liver Disease

PE-013

Seroprevalence of Anti-Hepatitis E Virus in the Patients with Autoimmune Hepatitis and Primary Biliary Cholangitis in South Korea

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Aims: The pathogenesis of autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) are unclear, but viral infection or environmental factor could trigger immune response in genetically predisposed individuals. Hepatitis E virus (HEV) was suggested as a potential trigger of AIH, but controversial results were reported. Moreover, the role of HEV in PBC was not reported. The aims of this study was to evaluate the seroprevalence of anti-HEV immunoglobulin G (IgG) in the patients with AIH and PBC compared to that in age- and sex-matched healthy controls in a South Korean tertiary hospital.

Methods: Using plasma samples obtained from prospectively enrolled patients with AIH (n = 43), PBC (n = 80), AIH-PBC variant (n = 8) and, and age-sex matched healthy controls (n = 50) in registry, anti-HEV IgG level was measured by commercial ELISA kit (Wantai, Beijing, China). Clinical data obtained from medical record were analysed.

Results: The mean age and female proportion (%) of AIH patients, PBC patients, and health control were 56 years (83%), 61 years (87%), and 59 years (88%), respectively. The seroprevalence of anti-HEV was 14%, 15%, and 16% in AIH, PBC and healthy controls, respectively. There was neither significant difference of anti-HEV prevalence between AIH and healthy controls, nor between PBC and healthy controls. The anti-HEV prevalence was only associated with increasing age and male sex in the above 3 groups. In the patients with AIH-PBC variant syndrome (mean age of 54 years, female proportion of 100%), there was no patient with anti-HEV positivity.

Conclusions: HEV infection seems to be not associated with AIH and PBC in Korean patients. However, further study with larger sample size is warranted.

Keywords: Hepatitis E virus, Autoimmune hepatitis, Primary biliary cholangitis, Anti-HEV IgG

PE-014

Histopathological Analysis and Validation of Different Scoring Systems for Autoimmune Hepatitis: Experience of Two Institutes

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Aims: The currently used criteria for autoimmune hepatitis (AIH) include the revised original (1999) and simplified (2008) scoring systems proposed by the international autoimmune hepatitis group (IAHG). Recently, new histologic criteria have been proposed (UCSF criteria). Here, we sought to evaluate the histological features of AIH according to the three proposed criteria.
Methods: Clinical data and liver biopsies were reviewed for 49 patients with AIH diagnosed at Seoul National University Hospital and Seoul National University Bundang Hospital between 2009 and 2014.
Results: Interface hepatitis (≥ Ishak Gr3), plasmacytic infiltrates, rosettes and emperipolesis were seen in 61.2%, 100%, 69.4% and 75.5%, respectively. Patients presented with cirrhosis in 22.4%, acute hepatitis pattern was seen in 38.8%, and co-existing steatosis was present in 34.7%. Except one patient with HBV hepatitis, the rest of patients met the 1999 IAHG criteria (65% "definite", 33% "probable"). Only 67.3% of those meeting the 1999 criteria also met the 2008 criteria (46.9% "definite", 20.4% "probable"). By the USCF criteria, definite/probable AIH increased from 67.3% to 83.7% (57.1% "definite", 26.5% "probable").
Conclusions: The concordance rate of 1999 IAHG and 2008 IAHG were 69%. The recently proposed UCSF criteria increased the diagnosis of AIH by 16.4%.
Keywords: Liver, Autoimmune hepatitis, Scoring

PE-015

Failing Transplanted Liver from an Unrecognised, Recently Discovered Autoimmunity Following HCV Eradication, What Options Do We Have?

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Aims: Unfortunately, recurrent HCV infection of engraftment is inevitable if the virus was not eradicated in recipients. Because of post-transplantation immunosuppression, if left untreated, HCV infection progresses to cirrhosis early in the post-transplant period. Direct antiviral agents (DAAs) has greatly improved the SVR (sustained virological response) rate, and safety concerns were minimal. Despite that a gray zone of mixed presentation of viral hepatitis with autoimmune hepatitis remains, posing a great challenge.
Methods: 47 years old man with living donor liver transplantation in October 2013, remained uneventful and was discharged on mycophenolate, mofetil and tacrolimus. He achieved SVR on Sofosbovir and Ribavirin therapy which was completed in December 2016. After 8 months of DAAs therapy he started noticing itching and mild fatigue, and on follow up he was found to have raised total bilirubin and alkaline phosphatase in December 2017. Although HCV PCR was negative and so was MRCP and other investigations.
Results: His liver biopsy revealed chronic ductopenic rejection with granuloma formation and features of autoimmune hepatitis. His ANA profile was found to be significantly positive. Despite steroids and further immunosuppression he could not manage to recover. He was sent to liver transplant centre for second liver transplant but concerns were reappearance of autoimmune flare and graft failure has limited his transplant.
Conclusions: This case is an eye opener for the transplant hepatologist and immunologist as autoimmunity remains to be to be a difficult scenario to cope with in transplant setting. Need powerful immunosuppressant in such cases and more insight into these grey zones.

Cell Biology / Molecular Biology

PE-016

Role of Momordica Charantia Fruit Extract against Hepatic Fibrosis Induced by Carbon Tetrachloride in Rats

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Aims: Momordica charantia Linn. (Karela) commonly known as Bitter melon or Bitter gourd is tropical and subtropical climber of the family Cucurbitaceae. Its fruit is also used for the treatment of diabetes and related conditions amongst the indigenous populations of Asia, South America, India and East Africa. Aim of present study was to investigate the *Momordica charantia* fruit (MCF) extract as hepaptoprotective agent verse hepatic damages caused by carbon tetrachloride (CCl4).
Methods: Male Wistar albino rats were divided into two equal groups (n = 8) and treated as follows: Group 1, kept as control group and orally given saline; Group 2, kept as control positive and were administered daily oral doses of MCF extract (150 mg/kg) daily for 21 days and subsequently injected i.p. with CCl4 (50% v/v in olive oil; 1 ml/kg) on the 22nd day. CCl4-induced damages were assessed through liver function markers viz; alkaline phosphatase, alanine transaminase, aspartate transaminase, and lactate dehydrogenase. Changes in lipid profile were checked by measuring serum total cholesterol, triglycerides, high density lipoproteins and low density lipoproteins. Antioxidant status was checked by the activities of antioxidant enzymes (superoxide dismutase, glutathione peroxidise), malondialdehyde (MDA)

content. The histopathological changes were observed with Masson staining.

Results: Administration CCl4 induced an elevation of serum amino- and glutamyl transferases activities and an increased peroxidation, as well as a decrease of superoxide dismutase and glutathione peroxidise activities in liver. Administration of CCl4 in rats caused significant increase in liver function and lipid profile indicating hepatic damages which were restored by co-administration of MCF extract. Cellular and DNA damages in hepatic tissues were caused by CCl4 which shown clear hepatic fibrosis in addition to disturb antioxidant enzyme level. Co-treatment with MCF extract regulated these markers of oxidative dysfunctions. *MCF* extracts enhances hepatic glutathione and may contribute to the antioxidant defense of the liver.

Conclusions: It may be conclude that MCF extracts have the ability to reverse CCl4 induced hepatic damages. *Momordica charantia* fruit has been used to treat alcoholic liver disease, acute and chronic viral hepatitis and toxin-induced liver diseases.

Keywords: Hepatic fibrosis, Momordica charantia fruit, Carbon tetrachloride, Rats

PE-017

Human Fetal Liver Cells as a Bridge to the Liver Transplantation in Patients Waiting for Donors

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Aims: The liver transplantation (LT) a method for treating liver cirrhosis. With a great increase in the death rate of patients with liver disorders, there is a necessity to pursuit for alternative therapeutic implement as supportive therapy. Recent studies show outstanding results in therapy using human fetal liver-derived stem cells (FLSC) and can deliver potentially to conservatively manage end-stage liver diseases. The present investigation aimed to study the safety and efficacy of FLSC transplantation.

Methods: 115 patients with liver cirrhosis of different etiologies were included in this study. All patients were on the waiting list and they were divided into 2 groups: received FLSC therapy and no treatment. FLSC were obtained from the fetus after an abortion by medical indications and were infused into the periphery. Liver function scores were chosen as endpoints to assess the efficacy.

Results: Child-Pugh score improved in 90 days in the cell therapy group. The model for end-stage liver disease score remained stable in the treated patients, whereas it increased during follow-up in the control group. Bilirubin levels increased among controls, whereas they decreased in the therapy arm during the first 60 days; INR RC differences between groups reached up to 10%. The changes observed did not persist beyond 90 days. There was marked clinical improvement observed in terms of all clinical and biochemical parameters. Further, there was a decrease in the mean MELD score observed in 6 months follow-up in all patients.

Conclusions: Transplantation of human FLSC into the periphery improved liver function in patients with advanced cirrhosis in the first 90 days. However, larger studies are necessary to define the role of human FLSC therapy in cirrhotic patients. Treatment by means of human FLSC proposals a potentially helpful modality to liver transplantation in the management such diseases.

Keywords: Liver, Fetal, Cells, Transplantation, Waiting list, Donors, Human, Stem cells

PE-018

Beryllium Induced Alterations in Liver Biochemistry and Histopathology: Reversal by Therapy of Aloe Vera with Piperine and Curcumin

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Aims: Beryllium is highly toxic to living system, induces oxidative stress, and alters major metabolic pathways. Thus, therapeutic efficacy of *Aloe vera* with piperine and curcumin were investigated against beryllium induced alterations liver biochemistry and utramorphology in rats.

Methods: $Be(NO_3)_2$ at doses of 1.0 mg/kg, i.p. once a day, daily for 5 weeks were administered in female *Wistar* albino rats followed by the treatment of *Aloe vera* (150 mg/kg, p.o) alone and in combination with piperine (2.5 mg/kg, p.o.), and curcumin (5.0 mg/kg, p.o.), once a day, daily for 1 week. Blood sugar, hepatic glycogen, G6Pase, SDH, G6PDH, Haemoglobin, bilirubin, ALAD, ALAS, AST, ALT, LDH, SALP, Albumin, markers of oxidative stress, and histopathogical alterations were monitored.

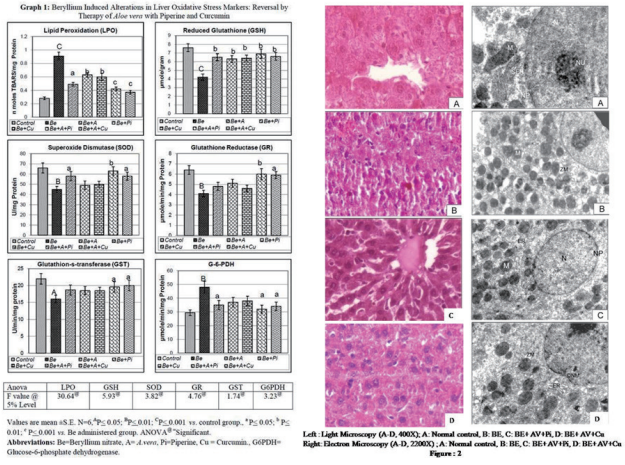
Results: Beryllium altered carbohydrate metabolism by decrease in blood sugar, glycogen, G-6-Pase and increase G6PDH activity. Beryllium disturbed heme biosynthesis by decrease in Hb and ALAD activity with increase in serum bilirubin and ALAS activity. Beryllium altered liver function by significantly increase in AST, ALT, LDH, and by significantly decrease in albumin, Succinate dehydrogenase (SDH) and SALP activity. Beryllium enhanced lipid peroxidation of biological membrane and depleted reduced glutathione. Antioxidants enzymatic activities of SOD, GR and GST decreased in beryllium intoxidation together with the deposition of beryllium in vital organs of rats. Beryllium altered the ultrastructure of liver. Therapy with *Aloe vera* showed improvement, however Combination of *Aloe vera* with piperine and curcumin were found better over monotherapy against beryllium induced altered liver function, oxidative stress, heme metabolism and restored the morphology of liver as seen by light microscopy and electron microscopy.

Conclusions: There is no significant difference observed between combination therapy of *Aloe vera* with Piperine and *Aloe vera* with curcumin, still combination of *Aloe vera* with piperine is considered better against beryllium intoxication if dose economy is concerned.

Table 1: Beryllium induced alterations in liver function, heme metabolism and carbohydrate metabolism: Reversal by therapy of *Aloe vera* with piperine and curcumin

Groups	ALT (IU/L)	AST (IU/L)	SALP (mg Pi/h/ 100ml)	HB (g/dl)	T.Bilirubin (mg/dl)	ALAD (nmole/min/l RBCs	ALAS (nmole/min/g liver)	Blood Sugar (mg/dl)	G-6-Pase (µmolePi/min/g liver)	SDH:Liver ($K_3Fe(CN)_6$ reduced/min /mg protein)
Control	48 ±2.84	70 ±4.65	190 ±11.54	16 ±0.93	0.40 ±0.02	9.8 ±0.71	7.2 ±0.36	117 ±6.78	7.2±0.60	48.0±3.3
Be *per se*	122 ±7.35[A]	121 ±6.88[A]	110 ±6.95[A]	12 ±0.93[A]	0.82 ±0.05[C]	4.8 ±0.40[A]	10.9 ±0.81[B]	62 ±4.16[A]	4.6±0.31[B]	22.5±2.06[C]
Be +A %Protection	90 ±5.77[B] 43.2%	103 ±5.73[B] 35.3%	132 ±8.05 27.5%	15 ±0.93[A] 75%	0.60±0.05[A] 50%	6.9 ±0.44[A] 42.0%	9.1±0.73 48.6%	80 ±5.47[A] 32.7%	6.1±0.33[B] 57.6%	32±2.82[A] 37.2%
Be + Pip	96 ±5.58[B]	102 ±6.13[A]	130 ±8.16	13.9 ±0.75	0.70 ±0.04	7.0 ±0.57[A]	8.7 ±0.50[A]	71 ±4.02	6.3±0.34[A]	29±2.39
Be +Cur	95 ±5.77[B]	100 ±5.77[B]	127 ±7.81	14.3 ±0.83	0.72 ±0.04	7.2 ±0.52[A]	8.8 ±0.54	90 ±5.77[B]	6.5±0.59[A]	31.5±3.19[A]
Be+ A+ Pi %Protection	78 ±4.89[B] 59.5%	86 ±5.53[B] 69.0%	161 ±10.64[B] 64.0%	15.7 ±0.90[B] 92.5%	0.50 ±0.03[C] 75.0%	7.5 ±0.50[A] 54.0%	7.4 ±0.41[A] 94.5%	98 ±7.48[B] 65.5%	6.9±0.50[A] 88.4%	42±2.92[C] 76.4%
Be+ A+ Cu %Protection	92 ±5.65[B] 54.0%	81 ±5.0[B] 78.5%	158 ±8.66[B] 60.0%	15.8 ±0.88[B] 95.0%	0.54 ±0.04[A] 65.0%	8.2 ±0.52[A] 68.0%	7.6 ±0.41[A] 89.1%	97 ±7.70[B] 64.0%	7.0±0.57[A] 92.3%	40.4±3.12[C] 70.1%
ANOVA (F Values)	16.13[D]	8.75[D]	9.09[D]	2.57[D]	9.27[D]	7.90[D]	5.1[D]	9.29[D]	3.07[D]	9.3[D]

Abbreviations: Values are mean ±S.E. N=6, [A]P≤ 0.05; [B]P≤0.01; [C]P≤0.001vs. control group., *P≤ 0.05; [b]P≤0.01; [c] P≤0.001 *vs.* Be administered group. ANOVA[@] [D]Significant. Be=Beryllium nitrate, A= *Aloe vera*, Pi=Piperine, Cu = Curcumin, ALT=Alanine transaminase, AST=Aspartate transaminase, SALP= Serum alkaline phosphatase, HB=hemoglobin, ALAD=ŏ-Aminolevulinic acid dehydratase, ALAS= ŏ-Aminilevulinic acid synthetase, G-6-Pase= Ghcose -6-phosphatase, SDH= Succinate Dehydrogenase.



Anova	LPO	GSH	SOD	GR	GST	G6PDH
F value @ 5% Level	30.64[D]	5.93[D]	3.82[D]	4.76[D]	1.74[ns]	3.23[D]

Values are mean ±S.E. N=6,[A]P≤ 0.05; [B]P≤ 0.01; [C]P≤ 0.001 vs. control group., *P≤ 0.05; [b]P≤ 0.01; [c] P≤ 0.001 vs. Be administered group. ANOVA[@] [D]Significant.
Abbreviations: Be=Beryllium nitrate, A= *A.vera*, Pi=Piperine, Cu = Curcumin., G6PDH= Ghcose-6-phosphate dehydrogenase.

Left : Light Microscopy (A-D, 400X); A: Normal control, B: BE, C: BE+ AV+N, D: BE+ AV+Cu
Right: Electron Microscopy (A-D, 22000X) ; A: Normal control, B: BE, C: BE+ AV+N, D: BE+ AV+Cu
Figure : 2

Keywords: Beryllium toxicity, Heme metabolism, Carbohydrate metabolism, Liver function test

PE-019

Histogenesis of Human Foetal Liver

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Aims: Liver is having the extensive power of regeneration is an important compound gland having both exocrine and endocrine functions. Its main function is to store glycogen. In foetal life, it is an important site of haemopoiesis. Though, detailed study of adult liver is there but microscopic structure of liver at different stages in the foetal period is far and few. Hence the present study aims to find out the histogenesis of liver in foetal period.

Methods: Dissection of 70 normal human foetuses was done from January 2015 to December 2018 and histological features of foetal liver tissue was studied by using H and E stain. Important findings of foetal liver were noted with respect to gestational age. PAS stain was used to observe the glycogen granules in the foetal liver. The size of hepatic lobule was measured by using an ocular and a stage micrometer. The distance was measured between the portal triad and central vein.

Results: In the foetal liver, central veins appeared first at 16th week, portal triad appeared at 18th week, hepatocytes are arranged around the central vein in the form of radiating cords giving a lobular pattern, efferent and afferent structures were present at the periphery of the lobule in the form of portal triad and it shows an extensive haemopoiesis in mid gestation. Glycogen appeared in hepatic cells was noted in 14th week. The size of hepatic lobule was 0.55mm in 16th week and 1.44mm at 38th week.

Conclusions: Our study on histogenesis of liver confirms the foetal haemopoietic function of liver regress towards the full term foetus at which the hepatocytes are occupied by plenty of glycogen deposits. It also provides new insights to the researchers and clinician for understanding the sequence of events in different weeks of gestation.

Keywords: Foetal hepatocytes, Haematopoiesis, Hepatic lobule

PE-020

High Maternal Linoleic Acid Alters Maternal Hepatic Cytokines and Circulating Lipid Profile in Rodent Model

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Aims: Linoleic acid (LA) is a polyunsaturated fatty acid which is essential and is only obtained in our diet. LA is critical during pregnancy for fetal development. The major sources of LA are vegetable oils and seeds. Due to increased dietary availability of LA in our modern diet, the consumption of LA has been increased gradually in the recent years. Studies have shown the detrimental effect of elevated LA in human health, however its effect on maternal health and fetal development during pregnancy is unknown. The main aim of this study was to explore whether high maternal LA affects maternal liver function, inflammation and fetal development.

Methods: Female Wistar Kyoto rats were fed with high LA diet (HLA-6.21% of energy) or low LA diet (LLA-1.44% of energy) with matched omega 3 (0.3% of energy), for 10 weeks prior to mating and during pregnancy. Animals were sacrificed at gestation day of 20 (E20), and maternal organs, maternal blood and fetal organs were collected for analysis. Circulating liver enzymes and lipid profile were estimated by fully automated biochemistry analyser and hepatic cytokines were measured by

Bio-plex assay.

Results: There were no significant differences in fetal and placental weights, however relative maternal liver weight was significantly increased in rats fed with HLA. There were no changes in maternal circulating cytokines, however, TNF-α and IL-7 levels were increased in the maternal liver from HLA rats. Circulating liver injury markers such as alanine transaminase, aspartate transaminase, albumin and total bilirubin were unchanged among the groups. Total cholesterol, LDL – cholesterol and HDL- cholesterol were decreased in the maternal plasma from rats fed with HLA.

Conclusions: HLA diet before and during pregnancy alters maternal lipid profile and liver cytokines suggesting that the amount of LA intake should be considered during pregnancy.

Keywords: Fatty acids, Linoleic acid, Hepatic cytokines, Maternal nutrition

PE-021

Diabetes Associated Liver Toxicity

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Aims: Pyrroloquinoline quinone (PQQ) is known to a strong antioxidant and has high free radical scavenging activities. It protects cells from oxidative stress-induced damage, effectively improves the activities of free radical scavenging enzymes and decreases the level of lipid peroxidation. Vitamin C and *S. cumini* seed extracts are also known to possess high antioxidative properties and can protect against several types of oxidative damages in diabetes mellitus. With respect to PQQ, nothing was known on its relative efficacy as compared to vitamins and plant extracts that possess antioxidant activity in any diseased condition. However, to its comparative effects in regulating diabetes associated hepatotoxicity, practically nothing has been studied so far. In the present investigation we evaluate and compare the ameliorating effects of PQQ with vitamin C and *S.cumini* seed extracts in STZ-induced diabetes mellitus with an emphasis on the oxidative stress in liver of mice.

Methods: Mice were randomly divided into five groups. Group I receiving only citrate buffer served as the normal control. Animals of groups II–V were rendered diabetic by single dose of streptozotocin (STZ, 150 mg/kg body weight), following which PQQ at a dose of 20 mg/kg, was injected to the animals of group III, while in group IV 50 mg/kg of vitamin C was injected and in group V animals *S.cumini* seed extract was injected 100 mg/kg for 15 days. At the end, alterations in different serum indices including glucose, lipid profile, urea, SGPT and SGOT; liver tissue peroxidation and antioxidants alterations; histopathological alteration in liver were evaluated.

Results: STZ-treated animals developed oxidative stress as indicated by a significant increase in lipid peroxidation, serum glucose, total cholesterol, triglyceride and urea, with a parallel decrease in the levels of liver tissue antioxidants. When diabetic animals received dose of PQQ, vitamin C and *S. cumini* in animals of group III, IV and V respectively, these adverse effects were ameliorated. However, 20 mg/kg of PQQ appeared to be more effective than vitamin C and *S.cumini* seed extracts.

Conclusions: These findings revealed for the first time that PQQ has the better potential than vitamin C and *S.cumini* seed extracts to mitigate diabetes associated oxidative damages in liver of mice.

Keywords: Diabetes mellitus, Liver, PQQ, Lipid peroxidation

PE-022

Effect of Gymnema Sylvestre on Liver Function Markers in Type II Diabetic Subjects

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Aims: *Gymnema sylvestre* have been used in the treatment of various problems for a long time in folk system of medicine. However, there are some reports in general state that, it has hepatotoxicity. Hence in the present study, we evaluated the effect of *Gymnema sylvestre* extracts on liver function markers in type II diabetic subjects.

Methods: Total of 50 subjects those who have type II diabetes were randomly selected from the week end diabetic clinic of Centre for Translation Research, Jiwaji University. The subjects have divided in to two groups to evaluate the antidiabetic activity and hepatotoxicity of *Gymnema sylvestre* aqueous extract and *Gymnema sylvestre* ethanol extract for 3 months. Biochemical parameters include fasting and PP blood glucose, glycosylated hemoglobin, liver function markers (Bilirubin, SGOT and SGPT), oxidative stress markers (SOD, Catalase, GSH, TBARS) were monitored in the study subjects. Paired t-test was used to compare the significance.

Results: Administration of *Gymnema sylvestre* extracts regularly for 3 months resulted in significant reductions of blood glucose ($P < 0.001$) and glycosylated hemoglobin levels ($P < 0.001$). The liver function markers (Bilirubin levels reduced 12.2-17.2% $P < 0.05$, SGOT levels reduced 15.8 - 17.1% $P < 0.05$ and SGPT levels reduced 14.7-17.3% $P < 0.05$ $P < 0.05$) and the antioxidant markers ($P < 0.05$) were also improved significantly.

Conclusions: *Gymnema sylvestre* extracts for the treatment of human type II diabetes mellitus show the significant improvement in glycemic control. The liver functions remained normal and in fact improved in many subjects. It may be due to the anti-oxidant property of the *Gymnema sylvestre*. Hence, Gymnema *sylvestre* extracts does not have any hepatotoxicity in the subjects.

Keywords: Hepotoxity, Gymnema sylvestre extracts, Liver enzymes, Type II diabetes

PE-023

Frequent Promoter Methylation and Gene Silencing of PTEN in Periampullary Carcinoma in Indian Population

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Aims: Periampullary carcinoma is a fast growing cancer usually detected in its advance stage. Molecular research on pancreatic cancer has discovered the role of both genetic and epigenetic changes in the occurrence of the disease. The aberrant DNA methylation may be proved as a promising biomarker for the diagnosis of periampullary cancer. Phosphatase and tensin homolog (PTEN) gene a well-known tumor suppressor gene located at 10q23.31., found to be frequently expressed in normal tissues and mutated in several types of cancers including. However, the role of loss of PTEN expression in association of promoter hypermethylation and spontaneous apoptosis and its impact on survival in periampullary carcinoma is not established.

Methods: One hundred and seven tumour tissues along with their nonadjacent tissues as normal from patients' undergone pancreaticoduodenectomy for periampullary carcinoma were analysed for the mutational, expressional, hypermethylation and apoptotic status of *PTEN* gene. Molecular profiling was performed by next generation sequencing, protein expression by immunohistochemistry, the methylation status by methylation specific PCR and Programmed cell death (apoptosis) by terminaldeoxynucleotidyltransferase biotin–dUTP nick end labelling (TUNEL) assay. The changes were correlated with clinicopathological characteristics, overall survival (OS) and recurrence free survival (RFS).

Results: Total 107 specimens (77 men, 30 women) were evaluated, 41(38) had well differentiated while 66 (62) had moderately or poorly differentiated tumors. Patient in their early stage T1 are having better survival as compared to stage T2 T3 and T4 with the significant *p*- value 0.017 while patients with positive lymph nodes showing poor survival in comparative with the patients with negative lymph nodes with $P = 0.047$. Further, those who not receiving adjuvant CTRT were shown to have better survival with highly significant $P = 0.00$. In-addition, patients with ampullary tumor were shown to have better survival than tumors of common bile duct, duodenum and head of pancreas with high significant $P = 0.00$. However, cases with recurrence were shown to have poor survival as compare to patients with no recurrence $P = 0.00$. The correlation of molecular parameters with clinicopathological characteristics showed significantly more loss of expression in ampullary tumours ($P = 0.06$) while significantly more hypermethylation ($P = 0.08$) and loss of apoptosis ($P = 0.06$) in patients with age >50years.

Conclusions: The loss of expression of PTEN gene is seen in ampullary subgroup of paeriampullary tumours. The promoter hypermethylation of *PTEN* gene and spontaneous apoptosis suppression in significantly more in older patients. PTEN gene loss did not have less impact on survival.

Keywords: Pten gene, Periampullary carcinoma, Methylation, Gene silencing

PE-024

Optimal Time and Condition of Hypoxic Preconditioning to Maximize Mesenchymal Stem Cell Function

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Aims: There are several reports that hypoxic preconditioning can enhance stem cell function. But the optimal time and condition of hypoxia of stem cell as well as its effect on function are still unclear. We investigated the characteristics of stem cells obtained from various hypoxic culture conditions (0.5–5% O_2) and normal oxygen culture conditions (21% O_2) to find out optimal culture conditions.

Methods: Cell viability and morphology were measured by MTT assay and trypan blue incorporation and cell number count assay in combination with normal and hypoxic culture conditions. In addition, the expression of major transcription factors, intracellular proteins, and paracrine factor of mesenchymal stem cells was confirmed by western blot and multiplex assay in various hypoxic culture conditions.

Results: Cell viability of hypoxic condition (0.5–5% O_2, and 24–48hr) slightly increased compared to normoxia, but there were significant differences. HIF-1α, a typical marker of hypoxia, increased in 0.5% and 1% O2 at 48 hours. We performed the whole cytokine array and compared the expression levels at each condition by selecting the factors which increased in hypoxic culture. Most of the factors that increased in hypoxic cultures were known to be important factors in neuronal cell growth and regeneration. The expression levels of angiogenin, IGFBP-2, MCP-1, IL-2Ra, VEGF-A and PDGF-BB were increased in hypoxia compared to normoxia. Cell proliferation was highest in 48h hypoxia (0.5% and 2% O2 concentration).

Conclusions: PDGF-BB, IGFBP-6, VEGF-A, NT-3 and angiogenin at 48 hours were increased in hypoxia (0.5% and 2% O_2).

Keywords: Stem cells, Hypoxia, Paracrine effect

PE-025

TRP2, a Prodrug of BMP7 Suppresses Hepatic Fibrosis in Mice Induced by the Treatment with Carbon Tetrachloride

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Aims: Hepatic fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation. Transforming growth factor-β (TGF-β) signaling plays a pivotal role in liver fibrosis via the activation of hepatic stellate cells in conjunction with hepatic cell death. Bone morphogenetic protein (BMP)-7, a member of the TGF-β superfamily, is an endogenous antagonist of TGF-β. In this study, we examined whether prodrug of BMP7 suppresses TGF-β signaling and its fibrogenic function in a murine model of liver fibrosis.
Methods: A liver fibrosis model was developed by the repetitive intraperitoneal injection of hepatotoxic carbon tetrachloride (CCl4) twice per week for up to 12 weeks. To investigate the therapeutic effect of BMP7 prodrug on hepatic fibrosis, mice received the drug at a dose 0 ug/kg (n = 10 for control), 50 μg/kg (low dose group, n = 8) and 500 μg/kg (high dose group, n = 10), respectively. Liver tissues were either snap-frozen in liquid nitrogen or fixed in 4% buffered paraformaldehyde for immunostaining.
Results: The aspartate and alanine aminotransferase levels were significantly decreased in BMP7 prodrug-treated groups compared to those in the control group (all $P < 0.05$). Fibrous septa surrounding liver parenchyma and marked bridging portal to portal with occasional were clearly seen in the control, while the treated groups showed only fibrous expansion of some portal areas with or without short fibrous septa. When fibrotic burden was graded according to *scoring system, fibrotic burden in TAT-BMP7 injected mice was significantly reduced when compared to that of control mice (all $P < 0.05$). In treated groups, mRNA expression levels of collagen 1A1, smooth muscle α-actin, connective tissue growth factor (CTGF) were significantly reduced compared to those in controls (all $P < 0.05$).
Conclusions: Our data demonstrate that TRP2, a prodrug of BMP7 can reduce hepatic fibrosis via suppressing TGF-β signaling.
Keywords: TRP2, BMP7, Hepatic fibrosis, Transforming growth factor-β

PE-026

Development of Doxorubicin-Incorporated Phenylboronic Acid Nanoassembly and Evaluation of Anti-Cancer Effect in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third highest cause of cancer-related death. Various therapeutic approaches have been proposed in an attempt to prolong survival of advanced HCC patients using different anti-cancer drugs or delivery systems. In this study, we investigated the ways to maximize the efficiency of delivery of anti-cancer drugs in HCC.
Methods: *In vitro* cytotoxicity of the nanocomplex with PBA conjugated doxorubicin (Dox), Dox and Phenylboronic acid (PBA) alone in various HCC cells was assayed by MTT assay. Using the xenograft and orthotopic model, the anti-cancer effect of nanocomplex was evaluated by measuring the tumor size and MR imaging. Serum AFP, ALT and creatinine levels were measured in those mice.
Results: The cytotoxicity of the nanocomplex increased dependent on its concentration. At low concentrations, nanocomplex showed higher cytotoxicity than DOX alone in HCC cells. On the other hand, PBA itself have no cytotoxicity in liver cells. *In vitro*, nanocomplex showed higher targetability in liver cancer cells by fluorescent imaging. *In vivo* experiments using bioimaging showed that the nanocomplex was more efficiently delivered to the tumor. In the Xenograft and orthotopic model, the tumor size in mice treated with nanocomplexes decreased than DOX alone group. In addition, serum AFP in nanocomplex group significantly decreased, but ALT and creatinine levels were within normal range. These results showed that nanocomplex exhibit better anti-cancer effects than DOX alone but does not cause liver and kidney toxicity.
Conclusions: The improved therapeutic effect of the nanocomplexes can be explained by active targeting via the enhanced cellular uptake by residual PBA moieties, and drug release in the intracellular environment. Nanocomplex have potent and specific anti-cancer effects on liver cancer cells. The overall results suggest therapeutic potential of pPBA-DOX nanocomplexes in liver cancer therapy.
This research was supported by BrainKorea 21.
Keywords: Hepatocellular carcinoma, Doxorubicin, Drug delivery system, Phenylboronic acid, Nanocomplex

PE-027

The Degree of HCC Differentiation Determines the Drug Diffusion in MCTS

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Aims: Hepatocellular carcinoma (HCC) treatment with multikinase inhibitor such as sorafenib is the most option for advanced HCC. Due to tumor heterogeneity, its efficacy greatly varies among patients and is limited due to adverse effects and drug resistance. Previous studies have shown that response to chemotherapy is highly affected by drug permeability through tumor tissue, highlighting the role of tumor microenvironment in cancer chemotherapy. As multi-cellular tumor spheroid (MCTS)

is superior to tumor cell monolayer culture in terms of mimicking tumor microenvironment, MCTS seems to be a suitable model for studying drug penetration into tumor.
Methods: To generate MCTS, HCC cells and stromal cells (LX2, WI38, and HUVECs) were mixed with 1:1 ratio at a density of 6×10^3 cells/well in 96-well round-bottom ultra-low attachment microplates. To generate cell lines stably expressing YAP/TEAD2DN, SNU449 and Hep3B HCC cell lines were maintained in media containing G418 disulfate salt following transfection with plasmids expressing individual DNA. For drug penetration study, fluorescent chemicals (e.g., verteporfin) were used and the distribution of drug within MCTS was determined by a LSM780 confocal microscope and LSR fortessa Flow Cytometry with a 425 to 440nm excitation and a 700 to 730nm emission filter set.
Results: Well differentiated SNU449 MCTS with low level of YAP/TAZ showed the least compactness of tumor spheroids, while Hep3B MCTS had the highest compactness with highest level of YAP/TAZ expression. Using stable cell lines, we confirmed the amount of verteporfin intercellular in SNU449-YAP MCTS were dramatically lower than SNU449-MCTS, while the amounts in Hep3B-TEAD2DN MCTS were dramatically higher than Hep3B-MCTS. HCC MCTS with higher YAP/TAZ levels increased the compactness and facilitated making a barrier to drug treatment.
Conclusions: In this study, diverse MCTS models have been developed using established HCC cell lines with different cell differentiation and stromal cells such as HSCs, fibroblasts, and endothelial cells. MCTS with poorly differentiated HCC showed an increased compactness of spheroids, an elevated level of YAP/TAZ and a limited drug penetration.
Keywords: Differentiation, MCTS, Drug penetration, Tumor microenvironment

PE-028

Knockdown of ATG7 Suppresses Tumorigenesis in HCC Mouse Models Induced by HRASG12V and shp53

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Aims: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults and the second leading cause of cancer-related deaths worldwide. Many studies showed that autophagy is associated with liver cancer. ATG7 is a critical component for the formation of autophagosome and thus required for autophagy processes. To investigate the effect of autophagy on liver cancer, we utilized ATG7 knock-down transgenic mouse models.
Methods: Transposon vectors encoding short hairpin RNA downregulating ATG7 (ATG7 shRNA) were constructed. Transposons encoding ATG7 shRNA were mixed with those encoding $HRAS^{G12V}$ and shp53 and then injected into the lateral tail veins of 5-week-old C57BL/6 mice. The development of liver cancer was observed grossly and histologically at 5-6weeks post hydrodynamic injection. Expression of genes related to autophagy process was assessed using western blotting and immunohistochemistry.
Results: We assessed knockdown efficiency of various ATG7 shRNAs in NIH3T3 cells. ATG7.1536 shRNA was most effective in downregulating ATG7. Mice were hydrodynamically transfected with transposons encoding shATG7 and then analyzed for tumor development in the liver. We found that the size and numbers of tumor nodules significantly decreased in the ATG7 knockdown groups compared to control. Histological examination of tumors from shATG7 mice showed knock-down of ATG7 and suppression of autophagic processes.
Conclusions: Knockdown of ATG7 led to a significant decrease in tumroigenesis induced by $HRAS^{G12V}$ and shp53. Inhibiting the autophagosome formation is expected to be a therapeutic option for liver cancer.
Keywords: ATG7, HCC, Autophagosome, Hydrodynamic transfection

Drug and Toxic Injury

PE-029

Effects of Anti-Tubercular Treatment on Liver in Newly Diagnosed Pulmonary Tuberculosis Patient on Intensive Phase of Treatment

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Aims: Tuberculosis (TB) still remains a major global health problem, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease. Due to its high morbidity and mortality, it's a major health problem despite of new and advanced methods of effective control programmes. The mainstay of treatment is anti-tubercular drugs, with undesirable adverse effects. Drugs implicated for anti-tuberculosis treatment (ATT) induced hepatotoxicity are Isoniazid, Pyrazinamide and Rifampicin are essential components of intensive phase of tuberculosis treatment. Aim of the research is to study the incidence and risk factor of hepatic damage and overt hepatitis in patients receiving anti-tubercular treatment as per DOTS(Directly Observed Treatment Short course) regimen and to halt the liver injury by early recognition of its adverse effects.
Methods: Prospective study conducted at Department of Internal Medicine Kaski Sewa Hospital and Research center Pokhara,

Nepal between February 2018-January 2019, 110 newly diagnosed pulmonary tuberculosis patients were given DOTS therapy as per National Tuberculosis Programme (NTP) guidelines (CAT I or II). Liver function tests were done before the initiation of therapy and repeated at 2nd, 4th and 8th week of treatment.

Results: In the present study group of 110 pulmonary tuberculosis patients from 14 – 75 years. 32 patients (29%) developed ATT induced liver injury which included 25 (23%) were asymptomatic and 7 (6%) patients who developed overt drug induced hepatotoxicity. 78% of cases > 60 years developed drug induced liver injury (DILI). Risk factor were heavy alcohol consumption 49%, Underweight (BMI) < 18.5-64%, low pretreatments albumin < 3.5% gm/dl- 58%. 7 cases who developed Drug induced Hepatotoxicity (DIH), drugs were stopped and later reintroduced.

Conclusions: Advanced age, heavy alcohol consumption, Underweight BMI < 18.5, and pretreatment hypoalbuminemia are predisposing factors for the development of ATT induced hepatotoxicity. Peak incidence of hepatitis occurs in the first month of therapy.

Keywords: Drug-induced liver injury, Hepatotoxicity, Tuberculosis, DOTS therapy

PE-030

Prevalence and Clinical Characteristics of Antibiotics Associated Drug Induced Liver Injury: From a Single Center Experience

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Aims: The use of antibiotics increases recently. Accordingly, the incidence of antibiotics associated with drug induced liver injury (DILI) also increases. The purpose of this study is to evaluate the proportion and the clinical characteristics of antibiotic associated with DILI.

Methods: This study is a retrospective study of analyzed adult patients who were referred to the department of hepatology for the elevation of liver function tests and the frequency of elevated liver enzyme of patients with prescribed antibiotics during the same period at outpatient setting as a validation set.

Results: Antibiotics associated with DILI (64.0%) are the most common reason agent among consulting to hepatology department. Rheumatoid arthritis related drugs (11.0%), health supplements (5.0%), herbal medicines (4.0%), anti-viral drugs, anti-inflammatory analgesics / acetaminophen and lipid-lowering agents (3.0%) were next common causative drug for DILI in inpatients setting (training set). The frequency of antibiotics associated with DILI was high in order of flomoxef, cetrazole, ceftriaxone, vancomycin, piperacillin/tazobactam and amoxicillin/clavulanate. In the same period, 32% of the patients who prescribed flomoxef showed elevated liver enzyme levels above the upper normal limit. The prevalence of flomoxef induced DILI (> 3 folds of ALT) was 13% and liver enzyme levels were five times higher than upper normal limits in 5% of flomoxef groups. Hypertension or diabetes was the risk factor of flomoxef associated with DILI.

Conclusions: The Prevalence of antibiotics associated with DILI was 2~14%. Co-morbidity with diabetes and hypertension was the risk factor of flomoxef associated with DILI.

Keywords: DILI, Antibiotics, Drug, Liver

PE-031

High Levels of Procalcitonin in the Early Phase after Pediatric Liver Transplantation Indicate Poor Postoperative Outcome

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Aims: To date, no data is available about procalcitonin (PCT) levels and its relevance to morbidity and graft function in the early phase after pediatric liver transplantation (pLTx). The aim of this study was to analyse the prognostic relevance of early postoperative PCT elevations in pediatric liver recipients.

Methods: Thirty pediatric patients who underwent 32 liver transplantations were included into this observational single-center study.

Results: Patients with high PCT levels on postoperative day (POD) 2 had higher International Normalized Ratio values on POD 5 ($P < 0.05$) and suffered more often from primary graft non-function ($P < 0.05$). They also had a longer stay in the pediatric intensive care unit ($P < 0.01$) and on mechanical ventilation ($P = 0.001$). There was no correlation between PCT elevation and systemic infection. However, PCT levels were correlated with peak serum lactate levels immediately after graft reperfusion and elevation of serum aminotransferases on POD 1 (r2=0.61, $P < 0.001$).

Conclusions: High levels of PCT after pLTx are an early indicator of poor postoperative outcome and may reflect ischemia induced liver cell injury within the context of an ischemia- reperfusion injury.

Keywords: Procalcitonin, Pediatric liver transplantation, Graft function, Serum lactate levels

PE-032

Cardiovascular Risk Factors after Conversion from Cyclosporine to Tacrolimus in Children after Liver Transplantation

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Aims: Calcineurin inhibitors (CNI) may increase the risk of cardiovascular (CV) events. This prospective study aimed to determine cardiovascular risk factors in pediatric patients after living related liver transplantation (LRLTx) 12 months after the conversion from cyclosporine (CS) to tacrolimus (TAC).
Methods: The study group consisted of 7 children (5 females and 2 males) after LRLTx performed at the median age of 3 years (range 0.8-7.2), who received CS monotherapy for at least 5 years before it was switched to TAC. The median age at conversion was years 13.1 years (range 10.1-18). Weight BMI Z-score, 24-h ABPM (ambulatory blood pressure monitoring), renal function assessment, and fasting lipid and oxidative stress profiles were performed before and 12 months after conversion.
Results: Within 1-year follow-up, TAC was well tolerated and we did not observe any drug-related adverse effects or severe infections. Renal function, blood pressure, and lipid parameters did not differ after the conversion. Before the conversion, there was lower median glutathione (GSH) levels (748 vs. 776 [µmol/l]) and glutathione peroxidase (GPx) activity (31.4 vs. 32.4 [U/gHb]), but statistical significance was not reached ($P > 0.05$). Asymmetric dimethylarginine (ADMA) levels were higher before conversion to TAC (0.93 vs. 0.69 [µmol/l], $P = 0.01$), as were oxidized LDL (oxyLDL) levels (317 vs. 264 [mU/ml], $P = 0.04$).
Conclusions: There was no significant difference between CS and TAC in risk factors for CV events. Potential benefits in oxidative stress profile resulting from CS to TAC conversion may add another important area for further research.
Keywords: Calcineurin inhibitors, Living related liver transplantation, Tacrolimus, Cyclosporine

PE-033

A Case of Toxic Hepatitis Induced by Noni Powder

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Aims: Toxic hepatitis could be caused by hepatotoxic drugs or metabolic intermediates and that result in liver cell injury. Although toxic hepatitis of various causes was reported, there was no case of toxic hepatitis caused by noni powder. The case we will report is a rare case of toxic hepatitis caused by taking Noni powder.
Methods: This abstract is case review.
Results: A 54-year-old male patient visited the hospital with jaundice and itching sensation. He has consumed daily 200g of the Noni for four months. We performed some laboratory tests and the results are as follows; Elevated liver enzymes, total and direct bilirubin, negative markers for viral diseases and negative tumor markers. Further tests, such as a rare liver disease autoimmune hepatitis and primary biliary cirrhosis were also negative. For hepatic parenchymal evaluation, liver biopsy was performed on the right lobe. As a result, toxic hepatitis was confirmed. Patient was treated with intravenous injection of hepatotonics, such as silymarin and biphenyl dimethyl dicarboxylate. Finally, the liver enzyme is normalized, and total serum bilirubin has been recovered.
Conclusions: The etiology of toxic hepatitis is varied, one is caused by the metabolites. This case is toxic hepatitis caused by Noni powder, which has never been reported in the past. There was no other cause of toxic hepatitis and we report a case with confirmed histopathology.
Keywords: Toxic, Hepatitis, Noni, Noni powder

Genetic

PE-034

Study on Validity of Biomarkers DKK1 and HBx-LINE1 in Diagnosis and Posttreatment Monitoring of Hepatocellular Carcinoma

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Aims: Evaluate validity of DKK1 and HBx-LINE1 in diagnosis and post-treatment of HCC/HBV and analyse relationship with clinical and paraclinical some characteristics.
Methods: Study on 114 HCC patients at 108 Military Central Hospital, 103 Military Hospital and 175 Military Hospital from 1/2016 to 3/2018 with DKK1 and HBx-LINE1, re-examination after surgery.
Results: With DKK1 ≥2,15 ng/mL, the positive rates of serum protein DKK1 were significant increased when compared with those of AFP (97.37% so với 62.92%). The mean of serum protein DKK1 of HCC was significant higher than it in liver cirrhosis patients with $P < 0.05$. Combination beetwen AFP and DKK1 expression will improved positive rates and help more diagnosis in 12.3% of HCC cases. Using combination of AFP, serum protein DKK1 and DKK1 expression may help diagnosis for negative AFP of HCC cases. Logistic regression analysis showed the risk of HCC will increased about 18.5 times when DKK1 ≥2,15 ng/mL. The level of DKK1 expression reduced in patients with ≥2 tumors when compare with one tumor and in cases with size ≥5 cm when compare with <5 cm. This correlation was the same with reducing of AFP related with quantity anf size of tumor. The level of DKK1 expressions reduced in posthepa-

tectomy when compare with those before surgery and in time of more than one year when compare with those from 1 to 12 months. We did not identify HBx-LINE1 fusion transcript in all 114 (100%) HBV-related HCC patients.

Conclusions: Biomarkers serum protein DKK1 and DKK1 expression have validity in diagnosis and post-treatment of HCC, especially for AFP-negative patient. HBx-LINE1 fusion transcript was not identified in our study.

Keywords: Hepatitis B virus, Hepatocellular carcinoma, Biomarker DKK1, Biomarker HBx-LINE1

PE-035

Research on PNPLA3 Gene in Patients with Type 2 Diabetes Mellitus and Accompanying Hepatic Pathology in Yakutia

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Aims: Studies of foreign and domestic scientists show the frequent combination of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (type 2 diabetes). The combination of these diseases aggravates each other, significantly increasing the likelihood of the patient developing liver fibrosis, hepatocellular carcinoma and cardiovascular diseases, as well as high mortality. Study of the frequency distribution of alleles among the Russian and Yakut population of the Republic of Sakha (Yakutia), as well as the search for associations of the polymorphic variant of the *PNPLA3* gene (rs738409 C> G) with liver diseases in patients with type 2 diabetes.

Methods: The study used DNA samples (n = 178) diagnosed with type 2 diabetes and concomitant liver diseases (the diagnosis is verified in medical organizations at the place of residence). The sample included 27 patients of the Russian and 151 patients of the Yakut nationalities. The comparison group was a sample of 135 healthy volunteers of Russian nationality and 246 healthy volunteers of Yakut nationality.

Results: Analysis of the frequency distribution of alleles and genotypes of the polymorphic variant of the *PNPLA3* gene (rs738409) in the studied samples showed the difference between Yakuts and Russians in both healthy volunteers and those suffering from liver diseases.

Conclusions: A significant difference was found between the frequencies of genotypes and alleles of the *PNPLA3* gene (rs738409) in russians and yakuts, both among healthy volunteers and in patients with type 2 diabetes with liver diseases. The frequency of occurrence of the G allele in the group of healthy yakuts was significantly higher (OR- 3.085; 95% CI: 2.260 - 4.210; $P < 0.001$) than in the group of healthy russians. When analyzing the distribution of frequencies of genotypes and alleles among a healthy sample and a sample of patients with liver diseases, both in the russian and yakut populations, no significant differences were found.

Keywords: Adioponutrin gene, Type 2 diabete, NAFLD, PNPLA3

HBV,Basic

PE-036

Ciclopirox Inhibits Hepatitis B Virus Secretion by Blocking Capsid Assembly

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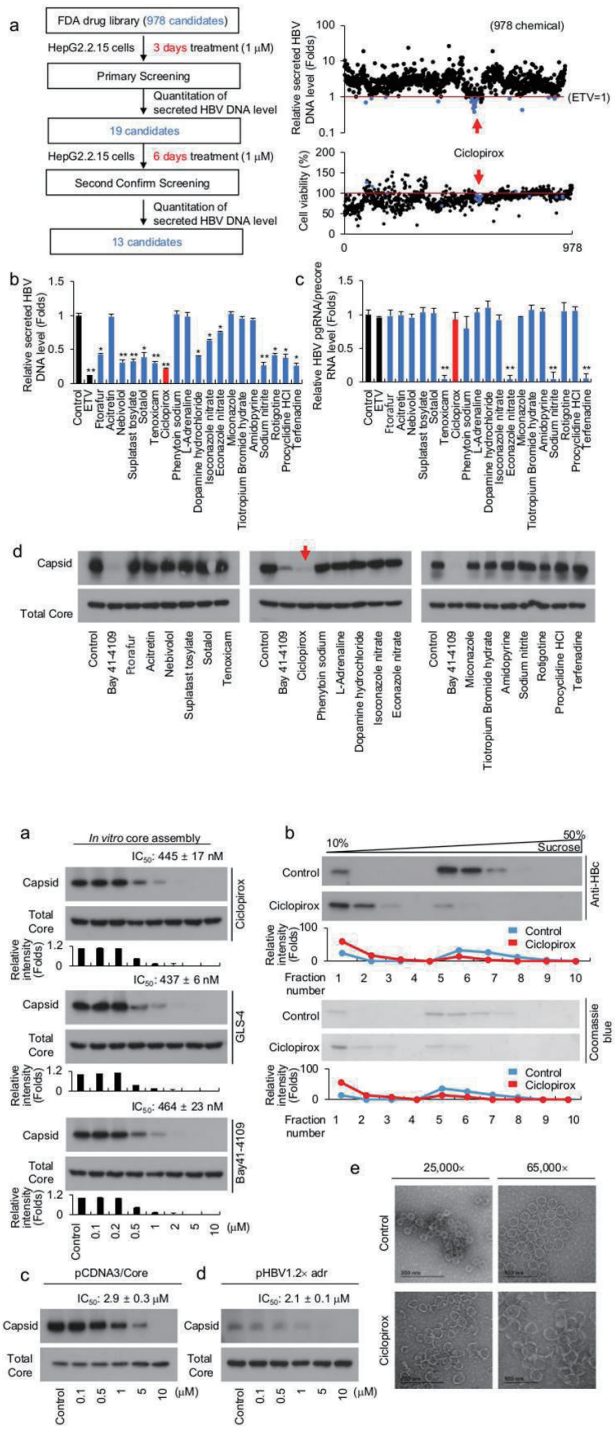
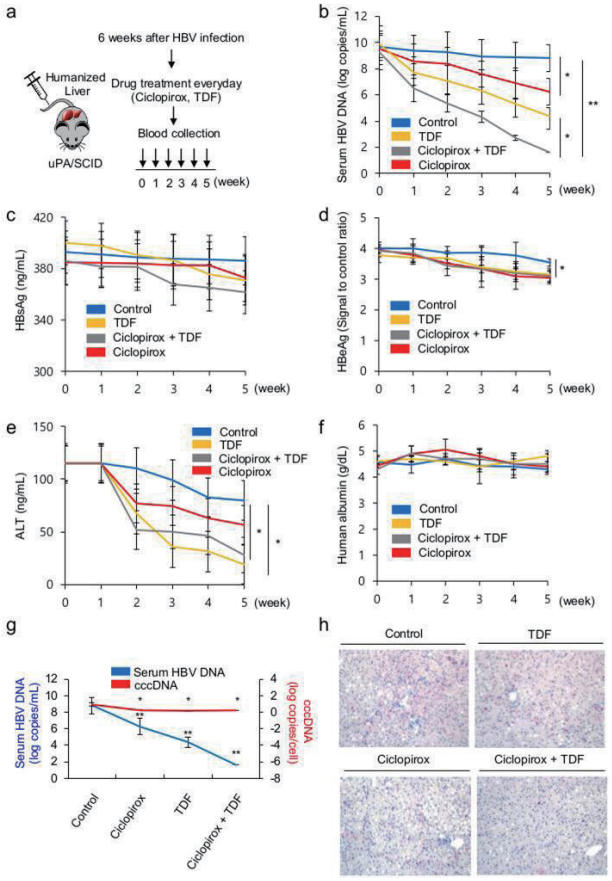
Aims: Chronic hepatitis B virus (HBV) infection can cause cirrhosis and hepatocellular carcinoma and is therefore a serious public health problem. Infected patients are currently treated with nucleoside/nucleotide analogs (NAs) and interferon a. However, this approach is not curative, and combined therapies that target multiple steps of the HBV life cycle are needed. Therefore, novel therapeutic agents are urgently required.

Methods: We screened 978 US Food and Drug Administration-approved compounds for their ability to inhibit HBV replication in HBV-expressing HepG2.2.15 cells. Quantitative PCR and southern blot analysis were performed to measure secreted and intracellular HBV DNA and intracellular cccDNA. Immunoblot analysis and electron microscopy were performed to analyze HBV capsid assembly *in vitro*. Human liver-chimeric uPA/SCID:PXB mice by PhoenixBio Co., Ltd. (Higashi-Hiroshima, Japan) were used for *in vivo* analysis.

Results: Ciclopirox, a synthetic antifungal agent, strongly inhibited HBV replication in cells and mice by blocking HBV capsid assembly. The crystal structure of the HBV core protein and ciclopirox complex revealed a novel binding mode at dimer-dimer interfaces. Ciclopirox synergized with NAs to prevent HBV replication in cells and in a humanized liver mouse model.

Conclusions: Orally-administered ciclopirox may block HBV capsid assembly effectively and thus provide a novel opportunity to combat chronic HBV infection.





Keywords: Hepatitis B virus, Capsid assembly, Ciclopirox, Antiviral

PE-037

cccDNA-Induced Hepatocarcinogenesis Is Regulated by HBx-Stimulated Interaction between MSL2 and cccDNA

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Aims: Hepatitis B virus (HBV) infection is a global health problem and chronic hepatitis B is the leading cause of hepatocellular carcinoma.The covalently closed circular DNA (cccDNA) is an intermediate in the life cycle of HBV virus.HBV-encoded X protein (HBx), a key viral oncoprotein, can be specifically modified by E3 ubiquitin ligase, such as Male Specific Lethal 2 (MSL2), a process called ubiquitination that up-regulates HBx activity to promote transcription, cell proliferation and tumor growth. This study aimed to compare the cccDNA, MSL2 mRNA and HBx mRNA levels in tumor and peri-tumor tissues, and explore the interaction between the level of cccDNA and MSL2 mRNA based on the HBx positive or negative. Moreover, we clarified the impact of antiviral therapy on these indicators.

Methods: The levels of intrahepatic cccDNA, MSL2 mRNA and

HBx mRNA in 50 patients with HBV-related HCC who had undergone liver surgery were compared.Real-Time PCR assay was performed to quantify these indicators.

Results: A total of 50 patients were included (49 HBsAg positive and 1 showing seroconversion after antivirus treatment). Before surgery, 31 of them had undergone antiviral treatment and 19 had not.Intrahepatic cccDNA levels ware significantly higher in the tumor tissues than in peri-tumor tissues (37/50, 74%; P = 0.001). The cccDNA level in the tumor and peri-tumor tissues was significantly different, especially in the HBeAg positive group (n = 14; P = 0.008), tumor recurrence group (n = 17; P = 0.002) and <3 cm tumor size group (n = 20; P = 0.003). The levels of cccDNA and MSL2 mRNA in the HBx positive group were significantly higher in tumor tissues than in peri-tumor tissues (n = 23; P = 0.026 and 0.015) . The level of HBx mRNA in antivirally treated peri-tumor tissues was significantly lower than that in untreated tissues (P = 0.010).

Conclusions: cccDNA may participate in the tumorgenesis of HBV-related HCC, a process regulated by the HBx-stimulated interaction between MSL2 and cccDNA. In addition, antiviral therapy may inhibit this process through reducing HBx levels.

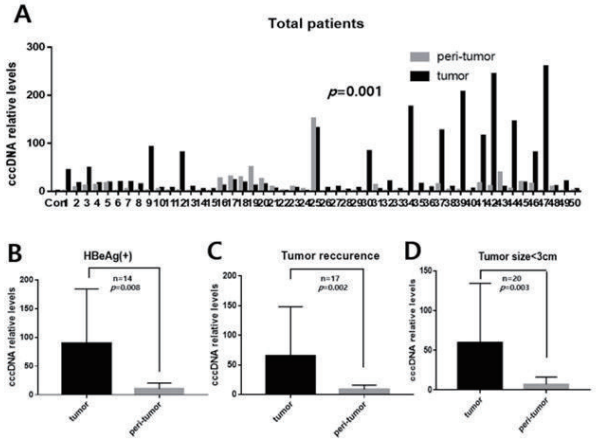

Fig. 1. Comparison of intrahepatic cccDNA in tumor and peri-tumor tissues of patients with HBV-related HCC. (A) Comparison of intrahepatic cccDNA levels in tumor and peri-tumor tissues of 50 patients; (B) Comparison of intrahepatic cccDNA levels in tumor and peri-tumor tissues of 14 HBeAg positive patients; (C) Comparison of intrahepatic cccDNA levels in tumor and peri-tumor tissues of 17 patients with HCC recurrence; (D) Comparison of intrahepatic cccDNA levels in tumor and peri-tumor tissues of 20 patients with tumor size of <3cm.

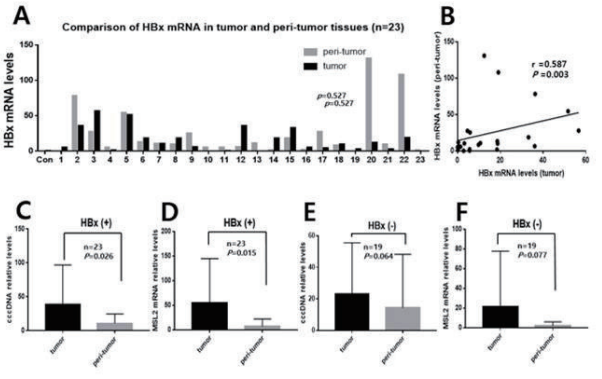

Fig. 2. The relative levels of HBx mRNA were examined in tumor and peri-tumor tissues using qRT-PCR (A) Comparison of relative HBx mRNA levels in tumor and peri-tumor tissues of 23 patient HBx positive; (B) Correlation of HBx mRNA between tumor and peri-tumor tissues; (C,D) Comparison of cccDNA and MSL2 mRNA in tumor and peri-tumor tissues of HBx positive patients; (E,F) Comparison of cccDNA and MSL2 mRNA in tumor and peri-tumor tissues of HBx negative patients.

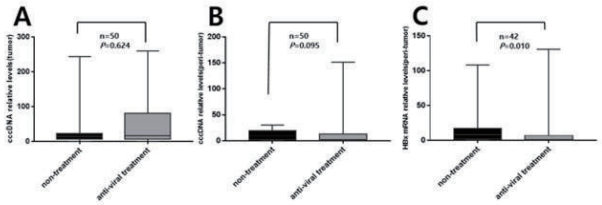

Fig. 3. Comparison of cccDNA/MSL2/HBx levels in tumor and peri-tumor tissues of patients receiving antiviral therapy and no antiviral therapy. (A) Comparison of cccDNA level in tumor tissues of patients with or without antiviral therapy; (B) Comparison of cccDNA level in peri-tumor tissues of patients with or without antiviral therapy; (C) Comparison of HBx mRNA level in peri-tumor tissues of patients with or without antiviral therapy.

Keywords: Hepatitis B, cccDNA, HBV DNA, HCC, MSL2, HBx, HCC recurrence

PE-038

The Effect of Living Donor Liver Transplantation on the Treatment of Severe Hepatitis

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Aims: To evaluate the effect of living donor liver transplantation on the treatment of severe hepatitis.

Methods: 18 patients with severe hepatitis received liver transplantation (transplanted severe hepatitis group), 28 patients with sever hepatitis received non surgical treatment (non-transplanted severe hepatitis group), and 30 patients with end stage liver cirrhosis (without cancer) received liver transplantation (transplanted cirrhosis group). The vital sign, blood coagulation, and renal function were monitored during operation. After liver transplantation, patients received immunosuppressive therapy (including tacrolimus or cyclosporine A, mycophenolate, mofetil and corticosteroids), intensive care, antiviral therapy (including lamivudine and HBIg) and other treatments (including restoration of liver function and prevention of blood coagulation). Pre-operation data, operation procedure, liver function, renal function and the operation complications of three groups were compared, and survival rate at 1, 6 and 12 months after operation was followed.

Results: There was no significant difference in the operation time, warm ischemia time, hypothermic ischemia time and Graft-to-recipient weight ratio between the two transplantation groups. The blood loss volume and blood transfusion volume in the transplanted severe hepatitis group were higher than that those in the cirrhosis transplantation group (t = 0.001, 0.004). The levels of TBil, ALT and AST at day 7 after operation were (100.5 +/- 96.4) mumol/L, (215.3 +/- 195.7) U/L, (209.8 +/- 188.6) U/L in the transplanted severe hepatitis group, and (53.3 +/- 31.9) mumol/L, (56.3 +/- 22.1) U/L, (51.3 +/- 13.5) U/L in the transplanted cirrhosis group (t = 0.017, 0.021, 0.004). However, there was no significant difference in the levels of Alb and Cr between these two groups (P > 0.05). Survival rate was 88.89%, 83.33% 83.33% in the transplanted severe hepatitis group, and 96.67%, 93.33% 93.33% in the transplanted

cirrhosis group at 1, 6 and 12 months after transplantation.
Conclusions: Living donor liver transplantation is one of effect ways for the treatment of severe hepatitis.
Keywords: Living donor liver transplantation, Liver cirrhosis, Immunosuppressive therapy, Severe hepatitis

PE-039

Costs of Viral Hepatitis B in the Republic of Korea, 2002–2015

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Aims: Even after the initiation of vaccination programs in 1990's, the positive rates for hepatitis B surface antigen in the Republic of Korea has remained at 3% level in recent 10 years. Despite the high prevalence and heavy burden of HBV infection, there have been no research on its costs reflecting the changes in application of the National Health Insurance Service (NHIS) coverage on antiviral drugs and recently revised guidelines regarding chronic hepatitis B management. The objective of this study is to estimate the economic burden of viral hepatitis B and trend of changes in its costs between 2002 and 2015.
Methods: Claims data from the NHIS which covers entire Korean citizens were used. To identify viral hepatitis B cases, the ICD-10th code B16, B17.0, B18.0, and B18.1 were used based on a primary diagnosis. This study was conducted from a societal perspective regarding both direct and indirect costs. Annual costs were adjusted for inflation by calculations based on the 2015 costs.
Results: The number of patients who made claims based on a viral hepatitis B diagnosis increased from 213,758 in 2002 (crude prevalence rate, 444.2 per 100,000) to 342,672 in 2015 (crude prevalence rate, 672.5 per 100,000). The total socioeconomic costs increased from 127.1 million USD in 2002 to 459.1 million USD in 2015. The healthcare costs for viral hepatitis B accounted for 0.13% of the national health expenditure in 2002, increasing to 0.31% in 2015. The pharmaceutical costs accounted for the largest proportion of total costs since 2009—220.5 million USD in 2015, which was approximately 15 times higher than that in 2002.
Conclusions: Among the socioeconomic costs of viral hepatitis B, healthcare costs have remarkably increased, mainly due to the increased costs of antiviral drugs. Therefore, effective policy and efficient management are needed to reduce the economic burden of HBV infection.
Keywords: Hepatitis B, Cost analysis, Antiviral drugs, Korea

PE-040

Knowledge and Practice of Hepatitis B and C among Medical and Health Science Students in Nepal

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Aims: Medical students like other health workers are being part of the health care delivery system are exposed to the same size of risk as other health care workers when they come in contact with patients and contaminated instruments. Knowledge of hepatitis B and C has been reported to be low among respondents in different studies. We conducted cross-sectional study among medical and health science students of Gandaki Medical College, Nepal to ascertain their knowledge and practices regarding hepatitis B and C.
Methods: A self-administered questionnaire consisting of questions to assess the knowledge and practice regarding hepatitis B and C infection, and perception of the medical students was duly filled by 48 students including first, second, third and fourth year. The data were entered and analyzed using Statistical Package for Social Sciences (SPSS) software version 25.
Results: Of the total 48 respondents, 29.2% were males and 70.8 females; 93.8% were unmarried. There was universal knowledge on causative agent, availability of preventive vaccines, transmission through infected needle or sharp object injury and liver cancer as its complication. Most of the students knew that hepatitis B could be prevented by vaccines however, 37% students mentioned that hepatitis C also could be prevented by vaccines. A 81.3% had proper knowledge about hepatitis B and hepatitis C could be prevented by proper disposal of needle and sharp instruments. Similarly, 83.3% had correct knowledge about mother to child transmission. However, about half of the respondents did not know hepatitis B and hepatitis C can be transmitted by sexual intercourse. Of the total, 85.4% respondents mentioned that hepatitis B and hepatitis C can not be transmitted from feco-oral route. Most of the students reported they used globes while handling different body fluids and did proper or disposal of needle and sharps. Of total, 25% had history of needlestick injury but only 4% reported for the injury. Of total, 16% students had been ever screened for hepatitis B or hepatitis C; 8% of the total had history of tattoo piercing practices.
Conclusions: Most of the respondents were aware about the hepatitis B and C, however, comprehensive knowledge on mode of transmission and preventive measures was lacking. Reporting after needlestick injury and screening for hepatitis B and C was low.
Keywords: Hepatitis, Knowledge, Practice, Students

HBV,Clinical

PE-041

Prevelance of Hepatitis Delta Virus Infection in Patients with Chronic Hepatitis B in Eastern Province Mongolia

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Aims: Hepatitis delta virus (HDV) is a serious cause of liver-related morbidity and mortality worldwide. The aim of our study was to determine the prevalence of HDV infection among patients positive for hepatitis B surface antigen (HBsAg) living in the Dornod province, which is in Eastern Mongolia.

Methods: Total of 251 HBV infected patients visiting the outpatient clinic at Dornod Medical Center from 2017 to January 2019 were screened for anti-HDV antibodies using ELISA assays. Anti-HDV-positive individuals were examined to determine HDV-RNA level by RT-PCR assay. Liver transaminases were analyzed using a commercial biochemistry kit.

Results: Of all patients, 115 were men (46%) and 136 were women (54%). The average age was 48 (between 16 and 70 years). Anti-HDV was positive in 73% (183/251) and all were checked for HDV RNA and 98% were found positive (179/183) all of the patients. Anti-HDV antibody positive patients showed significant liver cirrhosis higher (109/183) than Anti-HDV negative patients (16/68).

Conclusions: Our study showed hepatitis delta virus infection in HBsAg positive patients who live in Eastern province Mongolia higher than other provinces of Mongolia. Thus liver cirrhosis most related with positive anti-HDV patients.

Keywords: Hepatitis B virus, Hepatitis D virus, Prevalence

PE-042

Cases of the Influence of Mare's Milk on the Course of Viral Hepatitis B + D

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Aktobe Medical Center, Kazakhstan

Aims: Evaluate the effectiveness of mare's milk in viral hepatitis B + D.

Methods: The results of self-treatment of mare's milk in two patients with viral hepatitis B + D were studied. In both patients were examination for a PCR blood test and viral hepatitis B + D was detected. Fibroscan examination of the liver revealed fibrosis of 2–3 degrees. Patients refused to take antiviral drugs and were treated on their own by drinking mare's milk. Mare's milk was delivered to patients immediately after milking and was consumed daily in the morning for 200-300 ml during 6–8 months. Every month, patients underwent biochemical blood tests, serum tests for liver enzymes, a coagulogram, an ultrasound scan and liver fibroscanning. Once in every three months a blood test was performed on PCR for viral hepatitis.

Results: As a result of taking mare's milk, patients showed an improvement in their general condition. The data of monthly biochemical blood tests, the results of coagulogram showed minimal positive dynamics: a decrease in the level of hepatic enzymes, normalization of coagulogram were noted. Fibroscan of the liver did not reveal negative dynamics. A quantitative PCR blood test also showed a moderate reduction of the viral load.

Conclusions: Regular long-term usage of fresh mare's milk without antiviral drugs does not cause the progression of the development of viral hepatitis B + D. We believe that the use of mare's milk for viral hepatitis should be approached individually.

Keywords: Viral hepatitis, Mare's milk, Fibroscan, Influence

PE-043

A Large-Scale, Multi-Center Study of Entecavir vs. Tenofovir on Long-Term Prognosis for Treatment-Naïve Chronic Hepatitis B in the Republic of Korea

Seung Up Kim[1-3*], Yeon Seok Seo[4*], Han Ah Lee[4], Mi Na Kim[5], Yu Rim Lee[6], Hye Won Lee[1,3], Jun Yong Park[1-3], Do Young Kim[1-3], Sang Hoon Ahn[1-3], Kwang-Hyub Han[1-3], Seong Gyu Hwang[5], Kyu Sung Rim[5], Soon Ho Um[4], Won Young Tak[6], Young Oh Kweon[6], Beom Kyung Kim[1-3], and Soo Young Park[6]

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Aims: Which antiviral agent between entecavir (ETV) vs. tenofovir disoproxil fumarate (TDF) is superior in improving prognosis for chronic hepatitis B (CHB) is unclear. Here, we assessed the ability of these two antivirals to prevent liver-disease progression in treatmentnaïve CHB patients.

Methods: From 2012 to 2014, treatment-naïve CHB patients who received ETV or TDF as a firstline antiviral agent were recruited from four academic teaching hospitals. Patients with decompensated cirrhosis or hepatocellular carcinoma (HCC) at enrollment were excluded. Cumulative probabilities of HCC and death or orthotopic liver transplant (OLT) were assessed.

Results: In total, 2,897 patients (1,484 and 1,413 in the ETV and TDF groups, respectively) were recruited. The annual incidence of HCC was similar between the ETV and TDF groups

(1.92 *vs*. 1.69 per 100 person-years [PY], respectively; adjusted hazard ratio [HR], 0.975 [*P* = 0.852] by multivariate analysis). Propensity score (PS)-matched and inverse probability of treatment weighting (ITPW) analyses yielded similar results for both groups (HR, 1.021 [*P* = 0.884] and 0.998 [*P* = 0.988], respectively). The annual incidence of death or OLT was similar between the ETV and TDF groups (0.52 *vs*. 0.53 per 100 PY, respectively; adjusted HR, 1.202 [*P* = 0.451]). PS-matched and ITPW analyses yielded similar results for both groups (HR, 1.248 [*P* = 0.385] and 1.239 [*P* = 0.360], respectively). These findings were consistently reproduced in patients with compensated cirrhosis (all *P* > 0.05).

Conclusions: The risks of HCC and death or OLT were consistently similar between the ETV and TDF groups. Further studies are needed to validate our results.

Keywords: Entecavir, Tenofovir, Hepatocellular carcinoma, Prognosis

PE-044

Establishment of a Korean Chronic Hepatitis B Cohort Study

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Aims: Korea is endemic area of chronic hepatitis B (CHB), but there were few longitudinal, prospective cohorts to represent Korean patients with CHB. The aim of this study is to introduce Korean CHB cohort, and discuss future research focus. In addition, we demonstrated baseline characteristics of enrolled patients as intermediate results.

Methods: Korean CHB cohort was established in 2015 funded by the Korea Centers for Disease Control and Prevention. Five tertiary hospitals participated in this study. We collected patient's data from interview, self-questionnaires, laboratory test, imaging studies, and blood samples for research. Baseline characteristics was showed from October 2015 to May 2018.

Results: A total of 863 patients were enrolled from October 2015 to May 2018. Mean age was 50.4 ± 10.5, and the proportion of male patients was 61.9% (534/863). Hepatitis B e antigen positivity was 42.9% (370/863), and liver cirrhosis was 32.2% (278/863). The proportion of patients treated with antiviral therapy was 89.9% (783/863). Of these patients, 84.9% of patients was being treated with potent antiviral drugs such as tenofovir disoproxil fumarate, entecavir, tenofovir alafenamide, or besifovir.

Table 1. Baseline characteristics of Korean CHB cohort

Variables	N = 863
Age (years)	50.4 ± 10.5
Male gender, n (%)	534 (61.9)
BMI, kg/m2	23.9 ± 3.4
Current alcohol intake, n (%)	281 (32.6)
Current smoker/ Ex smoker, n (%)	168 (19.5) / 171 (19.8)
Family history of HBV (parents), n (%)	270 (31.3%)
HBeAg positivity, n (%)	370 (42.9)
Liver cirrhosis, n (%)	278 (32.2)
Platelet count, n/mm^3	182.6 ± 65.3
AST, IU/L	37.6 ± 68.2
ALT, IU/L	40.6 ± 69.0
Albumin, g/dL	4.3 ± 0.4
Total bilirubin, mg/dL	0.9 ± 0.6
PT-INR	1.0 ± 0.1
HBV DNA PCR, IU/mL	9,907,251.8 ± 89,910,000
HBV DNA <20IU/mL	535 (62.0)
FibroScan score, kPa	8.8 ± 8.6
FIB-4 > 3.25 / 1.45-3.25 / < 1.45	96 (12.8)/ 326 (43.5) / 327 (41.7)
APRI > 2.0 / 1.0 – 2.0 / < 1.0	33 (4.4)/ 62 (8.3) / 654 (87.3)
Antiviral therapy, n (%)	783 (89.9)
History of resistance to antiviral therapy, n (%)	169 (19.6)

Data are expressed as number (percentage) or mean ± standard deviation

Conclusions: This is a prospective, longitudinal nationwide cohort of CHB patients in Korea. Natural history and and long-term performance of antiviral therapy in Korean patients can be estimate using this cohort. In addition, unmet needs for CHB patients will be able to resolve through this cohort and blood samples.

Table 2. Types of antiviral drugs

Treated antiviral agents	N = 783
Peg-IFN	10 (1.3)
Lamivudine	20 (2.6)
Clevudine	5 (0.6)
Telbivudine	11 (1.4)
Adefovir	39 (5.0)
Entecavir	268 (34.2)
TDF	387 (49.4)
Besifovir	4 (0.5)
TAF	2 (0.3)
Clinical trial (besifovir or tenofovir)	4 (0.5)
Combination therapy	33 (4.2)

Data are expressed as number (percentage).

Table 3. Resistance to antiviral therapy

Variables	N = 169
Lamivudine only resistance	111 (65.7)
Adefovir only resistance	11 (6.5)
Entecavir only resistance	10 (5.9)
Lamividine + Adefovir resistance	7 (4.1)
Lamividuine + Entecavir resistance	24 (14.2)
Adefovir + Entecavir resistance	1 (0.6)
Lamivudine + Edefovir + Entecavir resistance	5 (3.0)

Data are expressed as number (percentage).

Keywords: Epidemiology, Chronic hepatitis B, Prospective, Korean cohort

PE-045

Projection of Health Outcomes over 5-Year and 10-Year Using Tenofovir Alafenamide for the Management of Chronic Hepatitis B in China

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Aims: The burden of chronic hepatitis B (CHB) infection in China is high, with an estimated 96 million patients. The goal of therapy is to suppress viral replication and achieve normalization of alanine aminotransferase (ALT) levels to reduce related liver complications such as compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC). In this study, we simulated the health consequences of nuecleos(t)ide analog (NA) therapies on 100,000 Chinese CHB patients comparing tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) and entecavir (ETV).

Methods: A health outcomes model was developed using an individual patient simulation framework. Model inputs were sourced from randomized controlled trials and peer-reviewed Chinese literature and validated by a panel of Chinese hepatologists. The model assumed that 90% of patients in the overall population were treatment-experienced (TE), of which 27% were assumed to have lamivudine (LAM) experience. The 5-year and 10-year risks for developing CC and HCC were calculated based on REVEAL score, taking into account early ALT normalization.

Results: Over the 5-year and 10-year period, patients treated with TAF were expected to experience less liver complications including CC, DCC, and HCC compared to TDF and ETV (Table 1). Specifically, compared to TDF and ETV, with TAF the rates of HCC were reduced by 13% and 31% over the 5-year projection.

Table 1: Percentage of Patients with Liver Complications over 5-Years and 10-Years (based on 100,000 simulated CHB patients)

	Over 5-years			Over 10-years		
Treatment Regimen	CC	DC	HCC	CC	DC	HCC
TAF	10.03%	0.66%	2.60%	12.15%	1.38%	4.49%
TDF	10.29%	0.69%	3.00%	12.89%	1.38%	5.84%
ETV	11.43%	0.88%	3.77%	16.44%	2.06%	8.50%

CC – Compensated Cirrhosis; DC – Decompensated Cirrhosis; HCC – hepatocellular carcinoma; ETV - Entecavir; TAF - Tenofovir Alafenamide; TDF - Tenofovir Disoproxil Fumarate;

Conclusions: TAF is projected to have fewer hepatic complications when compared to TDF and ETV over 5-year and 10-year time period, driven by its favorable efficacy and resistance profile.

Keywords: CHB, TAF, Tenofovir alafenamide, Health outcomes, HCC, TDF, ETV

PE-046

Lower Risk of Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients with Immune Tolerant Phase Than Those with Antiviral Therapy

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Aims: The risk of developing liver-related event (LRE) is controversial in chronic hepatitis B (CHB) patients with immune tolerant (IT)-phase. We compared the risk of developing LRE in CHB patients with IT-phase and those with antiviral therapy (AVT).

Methods: Consecutive patients with IT-phase and those with AVT between 2007 and 2017 were enrolled. IT-phase was defined as hepatitis B e antigen positive, HBV-DNA >20,000 IU/ml, and normal alanine aminotransferase (ALT, ≤40 IU/L). LRE included hepatocellular carcinoma (HCC), liver transplantation, or mortality.

Results: Of 125 (4.0%) patients with IT-phase, 46 (36.8%) stayed persistently in IT-phase, whereas the others experienced phase changes into inactive carrier (IC)-phase (n = 1, 0.8%) or minimally active (MA)-phase (n = 14, 11.2%), and immune active (IA)-phase with AVT (n = 64, 51.2%). The cumulative incidence of LRE was significantly lowest in patients with persistent IT-phase, middle in those with IT-phase at enrollment, but phase change into IA-phase with AVT, and highest in those with AVT (overall $P = 0.015$ in HCC and $P = 0.029$ in liver transplantation or mortality, log-rank test). When patients with IT-phase were censored at the time of phase change into IA-phase with AVT, the cumulative incidence of LRE was significantly low in patients with pure IT-phase than that of patients with AVT (both $P = 0.002$ for HCC and liver transplantation or mortality, log-rank tests).

Table 1. Baseline characteristics

Variables	All (n=3,108)	Patients with IT-phase (n=125, 4.0%)	Patients with AVT (n=2,983, 96.0%)	*P* value
Demographic variables				
Age, years	49.3 (39.8 - 56.8)	38.2 (28.1 - 50.8)	49.6 (40.3 - 56.9)	<0.001
Male gender	1878 (60.4)	48 (38.7)	1830 (61.3)	<0.001
Fatty liver	359 (11.6)	16 (12.9)	343 (11.5)	<0.001
Cirrhosis	959 (30.9)	--	959 (32.1)	--
Laboratory variables				
Platelet counts, 10^9/L	170 (122 - 221)	210 (179 - 261)	167 (120 - 219)	<0.001
Total bilirubin, mg/dL	0.8 (0.6 - 1.1)	0.7 (0.5 - 0.9)	0.8 (0.6 - 1.1)	<0.001
Serum albumin, g/L	4.2 (3.8 - 4.5)	4.4 (4.1 - 4.6)	4.2 (3.7 - 4.5)	<0.001
Aspartate aminotransferase, IU/L	45 (25 - 86)	23 (19 - 27)	46 (27 - 89)	<0.001
Alanine aminotransferase, IU/L	46 (23 - 104)	23 (18 - 31)	49 (24 - 108)	<0.001
Serum creatinine, mg/dL	0.82 (0.70 - 0.97)	0.82 (0.69 - 0.96)	0.82 (0.70 - 0.97)	0.496
Alpha-fetoprotein, ng/mL	4.35 (2.49 - 11.95)	1.87 (1.38 - 3.52)	4.53 (2.55 - 12.62)	<0.001
HBeAg positivity	1610 (51.8)	124 (100.0)	1486 (49.8)	<0.001
HBV-DNA, log IU/mL	5.45 (2.68 - 7.41)	8.04 (7.84 - 8.04)	5.31 (2.55 - 7.17)	<0.001

Variables are expressed as n (%) or median (interquartile range).
IT, immune tolerant; AVT, antiviral treatment; INR, international normalized ratio; HBeAg, hepatitis B e antigen.

Conclusions: CHB patients with IT-phase showed an extremely low risk of developing LRE than those with AVT. Thus, AVT should be cautiously considered for CHB patients with IT-phase.

Keywords: Immune tolerant, Hepatocellular carcinoma, Outcome, Antiviral therapy

PE-047

Real-Life Indication and Efficacy of Tenofovir Alafenamide, Tenofovir Disoproxil Fumarate, and Entecavir for Treatment Naïve Chronic Hepatitis B Patients

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Aims: Tenofovir alafenamide (TAF) is known to improve safety of chronic hepatitis B (CHB) patients with similar efficacy compared to tenofovir disoproxil fumarate (TDF), but the real-life outcome was not fully demonstrated. In this study, we aimed to elucidate the prescription pattern and real-life efficacies of TAF, TDF and entecavir (ETV) among CHB patients in Korea.

Methods: A total of 302 treatment-naïve CHB patients started TAF (n = 67), TDF (n = 131) or ETV (n = 104) were consecutively enrolled from Nov 2017 to Feb 2019. Presence of diabetes mellitus (DM), hypertension, dyslipidemia, and chronic kidney disease were determined by medical record and laboratory findings. Biochemical and virologic response rates and the change of glomerular filtration rate (GFR) during 6-month after treatment initiation were compared.

Results: Mean age of patients treated with ETV (57.7±10.6 y.o) was significantly older than TAF (47.1±11.2) or TDF (51.0±10.8, $P < 0.001$). ETV was more frequently prescribed in DM (55.6%, $P = 0.017$), CKD (48.8%, $P = 0.011$) or HCC (55%, $P < 0.001$) patients compared to tenofovir. Mean GFR change at 24 weeks-of-treatment from baseline were 3.7, -5.8, and 0.2 in TAF, TDF and ETV group, respectively ($P = 0.029$). Cumulative ALT and virologic response were not significantly different in 3 groups, but AST response rate was lower in TDF group (58.5% at 6 mo, $P = 0.034$ in HBeAg+; 53.9%, $P = 0.003$ in HBeAg-) compared with TAF (85%, 90.9%) or ETV (66.7%, 75%). According to multivariable Cox analysis, antiviral drug ($P < 0.0001$), underlying liver disease ($P = 0.051$) and DM ($P < 0.0001$) were independent predicting factors for AST response in HBeAg- patients.

Conclusions: In real-world practice, ETV was preferred in older, HBeAg- patients with DM or advanced liver diseases. Although antiviral drug prescription is decided based on patient's underlying disease which affected biochemical response, further large-scale study to confirm the favorable AST response with TAF is needed.

Keywords: Tenofovir alafenamide, Tenofovir disoproxil Fumarate, Entecavir, Chronic hepatitis B

PE-048

Association between Hepatitis B Virus Infection and Agent Orange in Non-Hodgkin's Lymphoma

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Aims: Hepatitis B virus (HBV) infection can be associated with non-Hodgkin's lymphoma (NHL). Agent Orange is also reported to cause NHL. However, a correlation between HBV and Agent Orange in NHL is not yet proven. The aim of this study was to investigate the association between HBV infection and Agent Orange who were diagnosed with NHL.

Methods: The authors reviewed 452 veterans patients with NHL from June 2003 to August 2018. A retrospective, case-control study was performed.

Results: Among 452 patients with NHL, 204 patients had been exposed to Agent Orange. The prevalence of hepatitis B surface antigen in 204 patients who had been exposed to Agent Orange (22 of 204; 10.9%) was significantly higher than that of 248 patients who had not been exposed to Agent Orange (8 of 248; 3.1%) (adjusted odds ratio, 3.6; 95% CI, 2.30-7.21). HBV carrier who had been exposed Agent Orange group (n = 22) presented with significantly more advanced liver disease and high HBV DNA level than those who had not been exposed Agent Orange group (n = 8). Among 30 patients with hepatitis B surface antigen who received anticancer therapy, 24 patients (86%) received prophylactic antiviral therapy, primarily lamivudine. There was no occurrence of hepatitis flare during antiviral therapy.

Conclusions: Agent Orange may have a significant correlation with HBV infection in NHL patients. Advanced liver disease and high HBV DNA level are more common in NHL patients who had been exposed Agent Orange.

Keywords: Hepatitis B virus infection, Agent Orange, Non-Hodgkin's lymphoma

PE-049

Comparable Incidence of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Treated with Entecavir or Tenofovir

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Aims: Adherence to medication and maintained virologic response (MVR) during antiviral therapy are related to decreased risk of adverse clinical outcomes. This study aimed to compare the efficacy of entecavir (ETV) and tenofovir disoproxil fumarate (TDF) in relation to the risk of hepatocellular carcinoma (HCC) and death or transplantation among chronic hepatitis B (CHB) patients stratified according to adherence to medication and MVR.

Methods: A total of 1794 treatment-naive CHB patients treated with ETV (n = 894) or TDF (n = 900) for >1 year were identified.

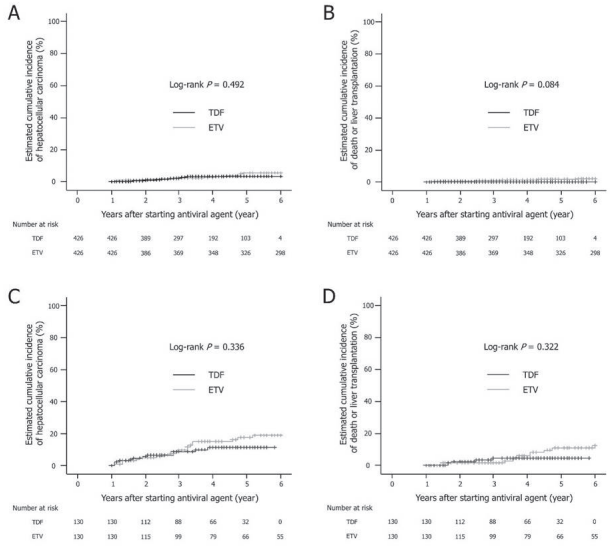

Figure 1. Cumulative incidence of hepatocellular carcinoma and death or transplantation according to initial antiviral agents used (TDF vs. ETV) in the propensity score matched patients among both the good and poor adherence groups. (A) Cumulative incidence of HCC in the good adherence group. (B) Cumulative incidence of death or transplantation in the good adherence group. (C) Cumulative incidence of HCC in the poor adherence group. (D) Cumulative incidence of death or transplantation in the poor adherence group.

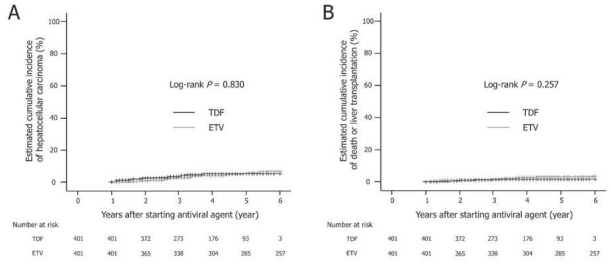

Figure 2. Cumulative incidence of (A) hepatocellular carcinoma and (B) death or transplantation according to initial antiviral agents used (TDF vs. ETV) in the propensity score matched group of patients with MVR.

Results: Adherence rates were significantly higher in the TDF group than in the ETV group (93.4% vs. 89.1%, respectively; $P < 0.001$). Multivariate analysis showed that the risk of HCC and death or transplantation was similar between groups (HR 0.826, 95% confidence interval (CI) 0.522–1.306; $P = 0.413$ and HR 0.636, 95% CI 0.258–1.569; $P = 0.325$, respectively) after adjusting for adherence to medication and MVR. In the 589 propensity-matched pairs of patients, risk of HCC and death or transplantation was similar between treatment groups. Moreover, the effects of ETV and TDF on clinical outcomes in matched pairs of patients stratified according to adherence rates and MVR were not significantly different.

Conclusions: The TDF group showed better medication adherence than the ETV group. However, after adjustment for adherence and MVR, ETV therapy and TDF therapy did not differ in terms of the risk of HCC and death or transplantation in all patients and propensity score-matched cohorts.

Keywords: Hepatitis B, Hepatocellular carcinoma, Liver cirrhosis, Antiviral therapy

PE-050

Frequent Radiological Assessment Using Computed Tomography Deteriorates Renal Function in Patients with HBV-Related Hepatocellular Carcinoma that Is Treated with Entecavir and Tenofovir

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Aims: Patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) frequently undergo radiological assessment using computed tomography (CT) and trans-arterial chemoembolization (TACE). Thus, we investigated whether frequent radiological assessment using CT or TACE additionally deteriorates renal function when various antiviral agents are used.

Methods: A total of 490 patients who were diagnosed with HBV-related HCC between 2001 and 2013 were enrolled. The main reasons for contrast use were CT and TACE during the follow-up period (medina 59.8 months).

Results: The median age of the study population was 54.8 years, and the male gender predominated (n = 394, 78.6%). A total of 284 (58.0%), 19 (3.7%), 156 (31.8%), and 32 (6.5%) patients received lamivudine, adefovir, entecavir, and tenofovir, respectively. On univariate analyses, CT evaluation ≥ 4 times/ year was significantly associated with progression in chronic kidney disease (CKD) stage ≥1 (hazard ratio [HR]=1.546, $P = 0.008$), along with increased age, hypertension, lower serum albumin, and longer prothrombin time (all $P < 0.05$). In addition, CT evaluation ≥ 4 times/ year was significantly associated with an increased risk of a reduction in the estimated glomerular filtration rate (eGFR) (<20% from the baseline) (HR = 1.394) and an increase in serum creatinine levels (≥25% from the baseline) (HR = 1.514) (all $P < 0.05$). In contrast, TACE was not associated with renal impairment ($P > 0.05$). After adjustment, CT evaluation ≥ 4 times/ year was found to be independently associated with an increased risk of disease progression in CKD stage ≥1 (HR = 1.533), reduction in eGFR (HR = 1.430), and increases in serum creatinine levels (HR = 1.536) in the entire

study population (all $P < 0.05$). When the study population was stratified according to administered antiviral agents, CT evaluation ≥ 4 times/ year was found to be independently associated with the increased risk of renal impairment only in patients treated with entecavir.

Conclusions: Frequent CT evaluation (≥ 4 times/ year) was significantly associated with renal impairment in patients with HBV-related HCC, especially in those treated with entecavir. Thus, radiological assessment using other imaging modalities, such as magnetic resonance imaging, or switching to other antiviral agents could be considered to prevent the progression of renal impairment.

Keywords: Computed tomography, Renal impairment, Hepatitis B virus, Antiviral therapy

PE-051

Low Incidence of Hepatitis B Reactivation after Kidney Transplantation in Hepatitis B Surface Antigen-Negative and Core Antibody-Positive Recipients

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Aims: Nowadays, intensive immunosuppression including rituximab is commonly used prior to kidney transplantation in patients who are ABO-incompatible and highly sensitized cases. Recent practice guidelines suggested antiviral therapy for the first 6-12 months, the period of maximal immunosuppression, may be considered for hepatitis B surface antigen (HBsAg) negative and anti-hepatitis B core (HBc) positive kidney transplant recipients. However, actual risk of hepatitis B virus (HBV) reactivation, and whether short-term antiviral therapy in early period is necessary remain unclear.

Methods: A total of 1294 consecutive patients who received kidney transplantation between 2007 and 2016 at Samsung medical center were screened. Among them, 454 HBsAg-negative and anti-HBc-positive kidney transplant recipients (median 51 years old, male: 63.4%, anti-HBs antibody (HBsAb) positivity: 86.6%, ABO mismatch: 20.9%, induction immunosuppressive therapy including rituximab: 15.0%) were analyzed for HBV reactivation during follow-up. HBV reactivation was defined as HBsAg reversion.

Results: During a median follow up of 6.7 (interquartile range: 4.1–9.4) years of 454 patients, HBV reactivation was observed in 7 patients (1.5%). All HBV reactivation occurred at least one year after transplantation (range: 17 – 53 months). There was no severe adverse outcome including jaundice, liver failure, liver transplantation or mortality. Only one patient showed severe hepatitis with peak alanine transaminase over five-fold of upper normal limit, but improved spontaneously before antiviral therapy. The risk of HBV reactivation did not differ according to age, sex, presence of HBsAb, ABO compatibility, use of plasmapheresis, induction with rituximab, or experience of rejection.

Conclusions: The risk of hepatitis B reactivation after kidney transplantation was low, and was not observed in early period after kidney transplantation. This data suggests that watchful monitoring without antiviral therapy would be sufficient, even for those who used rituximab.

Keywords: Hepatitis B, Reactivation, Kidney transplantation, Incidence

PE-052

Estimation of Hepatocellular Carcinoma Risk after Hepatitis B Surface Antigen Seroclearance

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Aims: Hepatitis B surface antigen (HBsAg) seroclearance. is considered as a functional cure of chronic HBV infection. However, available evidences suggest hepatocellular carcinoma (HCC) risk remains among patients with HBsAg seroclearance. We analyzed risk factors associated with HCC development in this population.

Methods: A retrospective cohort of 843 patients (median age: 57 years; males: 70.3%; cirrhosis: 14.1%; antiviral therapy (AVT) induced: 20.4%) who achieved HBsAg seroclearance were analyzed for the incident HCC during follow-up.

Results: During a median 3.6 years of follow-up (range: 1.0-12.3 years), HCC was developed in 13 patients (1.5%). All HCC cases were developed among patients who achieved HBsAg seroclearance after age of 50 years. Cirrhosis and elevated alanine aminotransferase (ALT) levels at HBsAg seroclearance were independent risk factors for HCC. The 5-years cumulative HCC incidence rate was 16.2%, 5.4%, 3.8% and 0% for cirrhotic patients with elevated alanine aminotransferase (ALT) levels, cirrhotic patients with normal ALT levels, non-cirrhotic patients with elevated ALT levels, and non-cirrhotic patients with normal ALT levels ($P < 0.001$). Notably, all HCC cases were identified among patients who achieved HBsAg seroclearance after age 50 years.

Conclusions: HCC risk was not *null* after HBsAg seroclearance, even among non-cirrhotic patients when ALT levels were elevated. Those with cirrhosis and elevated ALT levels warrants careful attention for remained HCC risk, even after HBsAg seroclearance.

Keywords: Hepatitis B, HBsAg seroclearance, Hepatocellular carcinoma

PE-053

Real-Life Efficacy of Glecaprevir and Pibrentasvir for Genotype 2 Chronic Hepatitis C

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Aims: Glecaprevir and Pibrentasvir (GP) are available for management of chronic hepatitis C (CHC) in Korea. The aim of the study is to evaluate the real-life efficacy of GP for genotype 2 CHC.

Methods: Since 2018, the patients who received GP at Korea University Medical Center were investigated retrospectively. We analyzed CHC patients with genotype 2 only in this study. The primary endpoint was sustained virologic response at week 12 post-treatment (SVR12). The lowest limit of HCV RNA detection was <15 IU/mL. Statistical analysis was performed by per-protocol (PP) basis. In addition, we compared the data with results of previous sofosbuvir plus ribavirin (SR) therapy at our institution (presented at the Liver Week in 2017).

Results: Total 147 patients were treated by GP regimen. 110 patients were excluded from analysis; 34 patients were non-genotype 2, and 76 patients' SVR12 data were not available since current initiation of treatment. At the present time, 37 patients were included for analysis. The median age was 55 (26-77) years (male, 45.9%). The median HCV RNA level was 602,000 (49-14,400,000) IU/mL. Two patients (5.4%) experienced previous directly acting antiviral failures (sofosbuvir). Patients with liver cirrhosis (21.6%) were treated for mean 11.8 ± 0.2 weeks while non-cirrhotic patients (78.4%) were treated for mean 8.0±0.2 weeks. The SVR12 was 100%. No patient showed treatment failure or relapse. Additionally, we compared the data with those of 122 genotype 2 CHC patients treated by SR at Korea University Medical Center until 2017 which showed 96.3% of SVR12 rate by PP analysis. There was no significant difference between 100% (GP) and 96.3% (SR) in SVR12 rate (P = 0.591).

Conclusions: The efficacy of GP regimen was excellent in real-life setting. Although the SVR12 rate of GP were not significantly different from that of SR, it was efficacious even in previous SR failures.

Keywords: Chronic hepatitis C, Genotype 2, Glecaprevir, Pibrentasvir

PE-054

Comparison of the Effect Tenofovir and Entecavir on Renal Function in Patients with Chronic Hepatitis B

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Aims: The effects of nucleos(t)ide analogs on kidney function in patients with chronic hepatitis B (CHB) are controversial. We aimed to compare the effects on renal function for tenofovir (TDF) and entecavir (ETV) in CHB patients.

Methods: We performed a retrospective cohort study of 357 consecutive treatment-naïve patients with CHB who were treated with TDF or ETV between January 2006 and March 2016. To assess renal function more accurately in the normal range, we used the recently validated, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to calculate the estimated glomerular filtration rate (eGFR).

Results: Two hundred one (56.3%) and 156 (43.7%) patients received TDF and ETV treatment, respectively. Liver cirrhosis (LC) was identified in 111 (31.1%) patients at the initiation of TDF or ETV treatment. Clinically significant (decrease of eGFR more than 20% compared to baseline) and persistent decrease in eGFR was noted in 26 (12.9%) and 7 (4.5%) patients in TDF and ETV treatment arm, respectively (P = 0.006). Advanced age, TDF treatment, presence of LC at baseline, higher baseline $\log_{10}$HBV-DNA level, and occurrence of hepatocellular carcinoma (HCC) and disease progression (PD) during antiviral treatment were significantly associated with the occurrence of clinically significant and persistent decrease in eGFR by univariate analyses. Multivariate analyses with adjustment of confounding variables including age and sex showed that TDF treatment (odds ratio [OR] 3.36, 95% confidence interval [CI] 1.38 ~ 8.13, P = 0.008), presence of LC at baseline (OR 4.22, 95% CI 1.88 ~ 9.47, P < 0.01), and higher baseline $\log_{10}$HBV-DNA level (OR 1.58, 95% CI 1.16 ~ 2.15, P = 0.004) were significant and independent contributors to the occurrence of clinically significant and persistent decrease in eGFR in patients with CHB who received TDF or ETV treatment.

Conclusions: TDF treatment adversely impacted the renal function in patients with CHB compared to ETV treatment.

Keywords: Renal adverse effect, Estimated glomerular filtration rate, Chronic kidney disease epidemiology collaboration, Tenofovir

PE-055

Comparison of Efficacy between Entecavir and Tenofovir in Treatment-Naïve Chronic Hepatitis B Patients with High Viraemia: Results from SAINT Cohort

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Aims: In treatment-naive chronic hepatitis B (CHB) patients with high hepatitis B virus (HBV) DNA (> 6 $\log_{10}$ IU/mL), there have been limited studies directly comparing the long-term efficacy between entecavir (ETV) and tenofovir disoproxil fumarate (TDF).
Methods: A total of 1,034 treatment-naïve CHB patients who received first line therapy with ETV (n = 487) or TDF (n = 547) were consecutively enrolled from 9 tertiary university hospitals in Korea between January 2012 and December 2015. Among total 1,034 patients, 396 patients were analyzed using propensity score matching, at a ratio of 1:1. 198 patients of each group were matched by age, baseline HBV DNA levels, cirrhosis, hepatitis B e antigen (HBeAg) status and comorbidity such as chronic kidney disease, diabetes mellitus and hypertension.
Results: Two groups showed no difference baseline characteristics. During the follow-up of 12 months, HBV DNA levels were similarly suppressed in both groups (ETV vs. TDF; -5.69 vs. -5.77 log10IU/mL, P = 0.516). In multivariate analysis, relatively low HBV DNA levels prior to treatment and initial virologic response at 3 months (IVR-3) were associated with VR at 1year. During long-term follow-up, HBV DNA levels were more strongly suppressed by TDF than ETV. However, multivariate analysis showed that HBeAg negative status, lower baseline HBV DNA and IVR-3 were independent factors for achieving VR. In subgroup analysis of HBeAg positive patients, the average time to achieve VR was shorter in TDF group than ETV (10.67 ± 5.83 vs. 15.01 ± 10.94, P = 0.000).
Conclusions: Although either ETV or TDF, overall, may show a comparable long-term antiviral efficacy in treatment-naive CHB, TDF might be better option than ETV to attain VR more rapidly, in HBeAg positive CHB patients with high HBV DNA levels.
Keywords: Entecavir, Tenofovir, Hepatitis B virus

PE-056

Fractures Related to Tenofovir Treatment in Patients with Chronic Hepatitis B: A Comparative Study in the National Database

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Aims: Tenofovir disoproxil fumarate (TDF) is a potent antiviral agent for the treatment of chronic hepatitis B(CHB). TDF is thought to be associated with bone loss. Herein, we aimed to assess the effects of exposure to TDF compared with entecavir (ETV) on the risk of osteoporosis-related bone fractures in patients with hepatitis B virus infection in South Korea.
Methods: We used claims data from the Korean National Health Insurance Database. Patients prescribed with antiviral agents, TDF or ETV, for CHB in 2013 were extracted. Data regarding prescribed drugs, comorbidities, and fractures were obtained. Osteoporosis-related fractures were identified using ICD-10-CM diagnosis codes for fracture. We assessed the incidence of fractures after TDF or ETV exposure from 2013 to 2015. Competing risk regression models were used to estimate hazard ratios (HRs) of fracture development.
Results: A total of 9748 patients over 20 years old with CHB who received TDF (n = 2713) or ETV (n = 7035) between January 2013 and December 2013 were enrolled in this study. Mean age was 50.4 years and 53.7 years in TDF and ETV group, respectively. The majority was male (77.1%; 74.1% in TDF group and 78.2% in ETV group). The incidence density of fracture per person-years was 0.99 in TDF group and 1.12 in ETV group. The median follow-up period in patients with fractures was 14 months in TDF group and ETV group, respectively.The hazard ratio (HR) for the development of osteoporosis-related fracture of TDF was 0.88 (95% confidence interval [CI], 0.64-1.21). The age and sex-adjusted HR was 1.02 (95% CI, 0.74-1.40).
Conclusions: Although TDF was reported to increase risk of osteoporotic fracture in patients with HIV infection, the present results based on relatively short-term follow-up data indicated that exposure to TDF was not significantly associated with a greater risk for fracture compared to ETV in patients with chronic hepatitis B. Further studies with long-term follow-up have to be awaited.
Keywords: National Health Insurance Claims data, Tenofovir, Fracture, Chronic hepatitis B

PE-057

Persistent Viremia after Entecavir Treatment and the Risk of Hepatocellular Carcinoma in Patients with HBV-Associated Cirrhosis

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Aims: The clinical significance of persistent viremia, which is defined as failure to achieve undetectable hepatitis B virus (HBV) DNA after 96 weeks of antiviral treatment, in cirrhotic patients treated with high resistant barrier drugs is not well known. This study investigated whether persistent viremia is associated with hepatocellular carcinoma (HCC) risk in patients with HBV-associated cirrhosis.

Methods: A total of 370 naïve patients with HBV-associated cirrhosis who were treated with entecavir (ETV), were retrospectively enrolled in 4 hospitals between March 2007 and December 2012. The clinical, laboratory data, persistent viremia, and non-invasive fibrosis markers [AST to platelet ratio index (APRI), FIB-4 index, fibrosis index] at 2-year treatment were analyzed for HCC development after 2-year treatment.

Results: After excluding patients who developed HCC within 2-year treatment, 359 patients (mean age 51±9, male 64.3%) were analyzed. During a median follow-up of 82 months, HCC developed in 80 patients (22.3%). In univariate analysis, older age (HR 1.06, 95% CI 1.03-1.08, $P < 0.001$), persistent viremia (HR 2.44, 95% CI 1.37-4.35, $P = 0.003$), lower albumin level (HR 0.47, 95% CI 0.31-0.72, $P = 0.001$), lower platelet count (HR 0.99, 95% CI 0.98-0.99, $P = 0.012$), higher FIB-4 index (HR 1.14, 95% CI 1.08-1.21, $P < 0.001$), and higher fibrosis index (HR 1.41, 95% CI 1.12-1.78, $P = 0.003$) at 2-year treatment were risk factors for HCC development. In multivariate analysis, older age (HR 1.05, 95% CI 1.02-1.07, $P < 0.001$), persistent viremia (HR 2.43, 95% CI 1.35-4.37, $P = 0.003$) and higher FIB-4 index (HR 1.10, 95% CI 1.04-1.18, $P = 0.002$) at 2-year treatment were independent risk factors for HCC development.

Conclusions: Old age, persistent viremia and high FIB-4 index at 2-year treatment were independent risk factors for HCC. Therefore, until anti-fibrotic agents are developed, control of persistent viremia may be needed to prevent HCC development.

Keywords: Persistent viremia, Cirrhosis, Hepatitis B virus, Hepatocellular carcinoma

PE-058

External Validation of the Modified PAGE-B Score in Asian Chronic Hepatitis B Patients Receiving Antiviral Therapy

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Aims: Modified PAGE-B (mPAGE-B) score including age, gender, platelet count and albumin as constituents was recently proposed to predict hepatocellular carcinoma (HCC) risk among chronic hepatitis B (CHB) patients undergoing antivirals. Here, in the independent cohort, we externally validated the predictive performance of mPAGE-B and compared it with those of conventional HCC prediction models.

Methods: We consecutively recruited CHB patients treated with lamivudine, entecavir, or tenofovir as the first-line antivirals. Patients with decompensated cirrhosis or HCC at baseline were excluded. Predictive performances of mPAGE-B and other models were assessed with comparison.

Results: Among 1330 patients, 9.6% developed HCC during follow-up (median 62.0 months). The mPAGE-B provided the highest Harrell's c-index (0.769), followed by GAG-HCC (0.751), PAGE (0.744), REACH-B (0.686), CU-HCC (0.618) and Toronto HCC risk index (THRI, 0.542). The mPAGE-B showed the similar performance to PAGE-B and GAG-HCC and the better performance than REACH-B, CU-HCC and THRI. Cumulative HCC probabilities at 5-, and 7-years were 0.0% and 0.0% in low-risk group (mPAGE score ≤ 8), 6.1% and 10.8% in intermediate-risk group (mPAGE score 9-12) and 18.7% and 26.7% in high-risk group (mPAGE score ≥ 13), respectively (both $P <$ 0.001 between low- vs. intermediate-risk groups and between intermediate- vs. high-risk groups). C-indices of mPAGE-B score were 0.785 and 0.724 among subgroups treated with entecavir or tenofovir (n = 1011) and with lamivudine (n = 319), respectively, which are overall similar to those of PAGE-B.

Conclusions: The mPAGE-B showed acceptable predictive performances. Compared to PAGE-B, addition of albumin as a constituent provided the marginal benefit in HCC risk prediction.

Keywords: Prediction, Hepatocellular carcinoma, Validation, Modified PAGE-B

PE-059

Tenofovir Disoproxil Fumarate versus Tenofovir Disoproxil for the Treatment of Patients with Chronic Hepatitis B Virus Infection

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Aims: Tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor and inhibitor of hepatitis B virus (HBV) polymerase, is the fumarate salt of the prodrug tenofovir disoproxil. After 2017, the patent on tenofovir disoproxil fumarate expired, a number of tenofovir disoproxil (TD) without salt of the active substance have been authorized. We compared the efficacy between TDF and TD in patients with chronic hepatitis B virus (HBV) infection in a non-inferiority study.

Methods: In a retrospective study we compared the efficacy of once-daily oral doses of TDF 300 mg (n = 53) and TD 245 mg (n = 59) in patients with chronic HBV infection. We assessed the

proportion of patients with HBV DNA <21 IU/ml, proportions of patients with HBsAg loss and seroconversion to anti-HBs, and, in the HBeAg-positive patients, proportions of patients with HBeAg loss and seroconversion to anti-HBe. Also we assessed ALT using normal ranges set by the central laboratory (Covance), and those set forth in the American Association for the Study of the Liver Diseases (AASLD) guidelines. The study was powered to show non-inferiority with a 10% efficacy margin of TD compared with TDF.

Results: From Jan 1, 2011 to Dec 31, 2017, 112 of treatment-naive patients were included and started receiving TDF 300 mg/d for median 53.9 months. Among them, 53 patients were continued receiving TDF 300mg/d and 59 patients were switched from TDF 300mg/d to TD 245mg/d between Jan 1, 2018 and Mar 31, 2018. 12(80%) of 15 patients receiving TDF had HBV DNA less than 21 IU/mL versus 10(91%) of 11 patients switching from TDF to TD (difference -1.1% [95% CI -4.1% to 1.9%]; $P = 0.47$), which demonstrates non-inferiority.

Conclusions: In patients with chronic HBV infection, the efficacy of tenofovir disoproxil without salt of the active substance was non-inferior to that of tenofovir disoproxil fumarate.

Keywords: Chronic hepatitis B virus, Tenofovir disoproxil fumarate, Tenofovir disoproxil, Efficacy

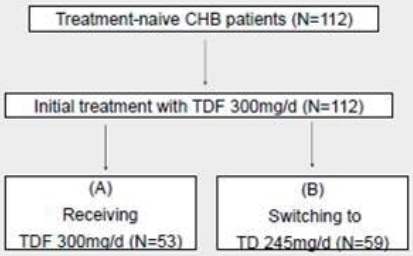
Table 1. Baseline characteristics.

	Treatment-naive CHB patients† (N=112)	Initial treatment with TDF 300mg (N=112)‡	
		(A) Receiving TDF 300mg/d (N=53)	(B) Switching to TD 245 mg/d (N=59)
Age, years	51.3 (25-77)	51.9 (29-77)	52.1 (25-75)
Sex			
Male	70 (63%)	31 (58%)	39 (66%)
Female	42 (37%)	22 (42%)	20 (34%)
Time to start TDF as first medical therapy, months (median)	5.2 (0-143154)	5.8 (0-143)	4.8 (0-47)
Duration of using TDF, months (median)	53.9 (12-85)	46.3 (21-80)	30.4 (12-85)
Duration of using TD, months (median)	-	-	14.1 (12-15)
Status of CHB, initial			
Without cirrhosis	55 (49%)	25 (47%)	30 (51%)
Compensated cirrhosis			
CTP-class A	49 (44%)	26 (49%)	23 (39%)
CTP-class B	7 (6%)	2 (4%)	5 (8%)
CTP-class C	1 (1%)	0	1 (2%)
Decompensated cirrhosis	0	0	0
Viral markers for hepatitis B			
Seropositive for HBeAg	60 (53%)	21	15
Seropositive for Anti-HBe	53 (47%)	31	39
HBV-DNA (log_{10}IU/mL)	7.23	2.75	1.72
Blood chemistry			
ALT (U/L)	133	49	29
ALT concentration > ULN by central lab criteria	89 (79%)	19 (36%)	7 (12%)
ALT concentration > ULN by AASLD criteria	81 (72%)	13 (25%)	6 (10%)
eGFR by Cockcroft-Gault (mL/min)	100.0	91.2	98.5
eGFR by CKD-EPI (mL/min)	97.2	91.2	96.8

Table 2. Comparison of efficacy outcomes.

	At the time of dividing into two groups (N=112)	(A) Continue receiving TDF 300mg/d (N=53)	(B) Switching to TD 245mg/d (N=59)	Difference in proportions (95% CI) between (A) and (B)	p value
HBV DNA < 21 IU/mL¶	86/112 (77%)	12/15 (80%)	10/11 (91%)	-1.1% (-4.1% to 1.9%)	0.47
HBeAg loss*	14/52 (27%)	13/21 (62%)	3/17 (18%)	1.4% (1.5% to 7.4%)	0.00
HBeAg seroconversion*	12/52 (23%)	12/22 (55%)	2/18 (11%)	4.3% (1.7% to 7.0%)	0.00
HBsAg loss†	0	0	0	-	-
HBsAg seroconversion†	0	0	0	-	-
Normalized ALT by central laboratory normal range‡	66/89 (74%)	11/19 (58%)	5/6 (83%)	-2.5% (-7.1% to 2.0%)	0.24
Normalized ALT by AASLD normal range§	29/81 (36%)	3/12 (12%)	3/5 (60%)	-3.5% (-1.0% to 3.2%)	0.25

Figure 1. Flow chart of selection of patients with CHB.



PE-060

Efficacy and Safety of 3-Year Entecavir and Tenofovir Therapy in Chronic Hepatitis B Patients with Chronic Kidney Disease: A Multicenter, Retrospective Cohort Study

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Aims: We investigate the efficacy and safety of entecavir (ETV) versus tenofovir (TDF) in treatment-naïve chronic hepatitis B (CHB) patients with chronic kidney disease (CKD) in real life setting.

Methods: A total of 1,737 naïve CHB patients treated with ETV or TDF at least 1 year in 9 academic hospitals from Jan. 2011 to Dec. 2015 were enrolled. Data of 44 patients with CKD of enrolled patients were collected retrospectively. CKD was defined as glomerular filtration rate <60ml/min/1.73m^2. Renal functional decline was defined when serum creatinine level increased by more than 50% from baseline or over than 0.3 mg/dL at each year.

Results: A total of 47 patients (ETV 34 and TDF 13) were followed up for a median 56 months (range 12-93). There were no significant differences in cumulative biochemical response rate and culmulative HBeAg seroconversion rate between the ETV group and the TDF group at months 6, 12, 24 and 36 of treatment. However, there were significant differences in culmulative virologic response rate between the ETV group and the TDF group at months 6, 12, 24 and 36 of treatment (38.2%/61.8%/82.4%/88.2% *vs.*69.2%/84.6%/92.3%/100%, P = 0.042). Renal functional decline at months 12, 24 and 36 occurred in 29.5%/31.4%/36.6% of patients. Renal functional decline showed no significant difference between the ETV group and TDF group. Multivariate analysis showed that HBeAg negativity, lower baseline HBV DNA, higher baseline ALT and TDF regimen were independent factors for achieving virologic response.

Conclusions: TDF had better clinical efficacy than ETV in CHB patient with CKD. TDF had not significantly higher risk for the development of renal insufficiency than ETV. This study suggests that TDF may be a better option than ETV in CHB patient with CKD.

Keywords: Chronic kidney disease, Efficacy, Antivirals, Safety

PE-061

Real World Data of Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate for the Treatment of Patients with Chronic Hepatitis B

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Aims: We compared the efficacy and safety of the two drugs in patients with chronic hepatitis B (CHB).

Methods: Patients with CHB treated with tenofovir alafenamide (TAF, n = 105) or tenofovir disoproxil fumarate (TDF, n = 105) in two tertiary referral centers between November 1, 2017, and December 31, 2017, were analyzed. Eligible patients were aged at least 18 years with chronic HBV infection (with serum HBV DNA concentrations of >2,000 IU/mL), serum alanine aminotransferase concentrations of greater than 40 U/L and at no more than twenty times the upper limit of normal, and estimated glomerular filtrate rate (eGFR) of at least 50 mL/min (by the Chronic kidney disease epidemiology collaboration). The primary efficacy endpoint was the proportion of patients who had HBV DNA less than 20 IU/mL at week 48; Serum phosphorus, eGFR and lipid profile were assessed to evaluate the safety.

Results: Baseline characteristics were not different between the two groups. Biochemical response (ALT<40 IU/L) rate in TAF and TDF group was 79.8% (71/89) vs 86.6% (84/97) at 24 weeks, 82.2% (37/45) vs. 81.5% (53/65) at 48 weeks. Virological response rates (HBV DNA <20 IU/mL) was 34.5% (29/84) vs. 34.5% (31/90) at 24 weeks, 61.0% (25/41) vs. 66.1% (37/56) at 48 weeks. There were no statistical differences in biochemical and virological response rates. The mean reduction in serum HBV DNA from baseline to 24 and 48 weeks were similar in TAF and TDF group (-5.0 vs -5.3 and -5.3 vs -5.5 log10 copies/mL, P = 0.132). HBeAg seroconversion was 3.0% (2/66) vs 2.8% (2/71) at 48 weeks. Virological breakthrough was not seen in both groups. At week 48, mean change in eGFR was similar in both groups (TAF -4.4 mL/min vs TDF -5.4 mL/min; P = 0·766), mean change in phosphorus was also similar in both group (TAF -0.07 mg/dL vs TDF -0.04 mg/dL ; P = 0·781), but mean change in total cholesterol was slightly elevated in TAF group (TAF +0.86 mg/dL vs TDF -12.3 mg/dL ; P = 0.057).

Conclusions: In patients with HBeAg positive and negative CHB, the efficacy and safety of TAF were similar to those of TDF at 48 weeks. However, TAF is likely to induce dyslipidemia.

Keywords: Chronic hepatitis B, Tenofovir disoproxil fumarate, Tenofovir alafenamide, Dyslipidemia

PE-062

The Effectiveness of Tenofovir and Hepatitis B Immunoglobulin in Preventing HBV Vertical Transmission for Pregnancy

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Aims: To evaluate the efficacy and safety of tenofovir (TDF) and hepatitis B Immunoglobulin for preventing hepatitis B virus (HBV) vertical transmission for HBV-positive pregnant women.

Methods: Pregnant women (n = 47) from January 2016 to June 2018 visiting the outpatient clinic, were enrolled when they met inclusion criteria, which included HBV DNA ≥200000 IU/mL and increased alanine aminotransferase (ALT) levels. All patients were treated with TDF. All infants were vaccinated with hepatitis B immunoglobulin and HBV vaccine. Vertical transmission of

HBV was indicated by the presence of hepatitis B surface antigen (HBsAg) in infants 6 months and 12 months after birth.
Results: Their mean HBV DNA 350000 IU/mL and mean alanine aminotransferase (ALT) levels were 56 U/L. after anti-HBV treatment in patients were significantly decreased HBV DNA (54000 IU/mL), ALT levels were 34 U/L. The HBsAg positivity rates of infants at postpartum 24 weeks and 48 weeks was 0% respectively ($P < .001$).
Conclusions: Administration of TDF to HBV-infected mothers and infants to hepatitis B immunoglobulin are effective and safe to block mother-to-infant HBV transmission.
Keywords: Preventing, Tenofovir, Pregnant women

PE-063

Cumulative Incidence of Hepatocellular Carcinoma and Hepatitis B Surface Antigen Seroclearance after Nucleos(t)ide Analogue Induced Hepatitis B e Antigen Seroclearance

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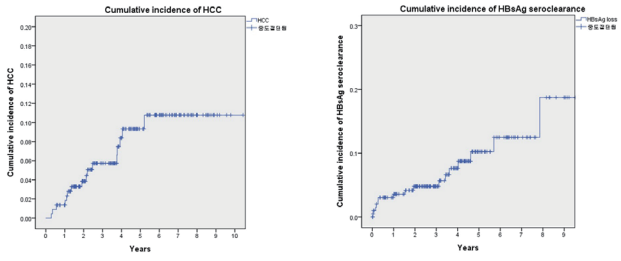
Aims: Hepatitis B e antigen (HBeAg) seroclearance in the long term has been viewed as a treatment endpoint and a measurement of treatment success. We tried to determine the clinical outcomes for hepatocellular carcinoma (HCC), and hepatitis B surface antigen (HBsAg) seroclearance of patients undergoing nucleos(t)ide analogue induced HBeAg seroclearance.
Methods: The current study included patients who required antiviral treatment (entecavir or tenofovir) before and/or after HBeAg seroclearance, within a tertiary care setting. Patients with documented HBeAg seroclearance were followed up 6-monthly. Baseline characteristics and longitudinal laboratory results were recorded.



Results: Cumulative incidence for HCC and HBsAg seroclearance were derived from Kaplan-Meier method. A total of 219 patients underwent HBeAg seroclearance with a median age and follow-up of 50 and 4.2 years, respectively. The cumulative incidence of HCC and HBsAg seroclearance was 10.8% and 18.7% at 9 years after HBeAg seroclearance, respectively.
Conclusions: A small proportion of patients who undergo nucleos(t)ide analogue induced HBeAg seroclearance achieved HBsAg seroclearance. However, a significant proportion of patients will develop hepatocellular carcinoma after HBeAg seroclearance.
Keywords: HBeAg seroclearance, HBsAg seroclearance, Hepatocellular carcinoma, Chronic hepatitis B

PE-064

Clinical Impact and Correlation of Serum HBV DNA and HBcrAg Titer in Patients with Chronic Hepatitis B during Antiviral Therapy

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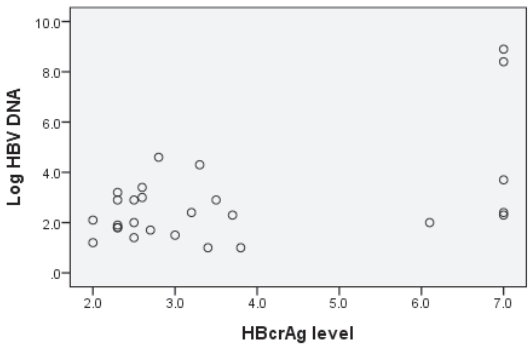
Backgrouds and Aim: The HBcrAg assay detects the sum of hepatitis B core antigen (HBcAg), e antigen (HBeAg) and its related byproduct, 22-kDa precore protein (p22cr). It was proposed as a surrogate marker for HBV persistence. We aimed to evaluate the correlation with HBV DNA and HBcrAg level in patients with chronic hepatitis B (CHB) during antiviral therapy.
Method: This study included 27 patients with CHB who were hospitalized at Gangnam Severance Hospital between March 2019 and April 2019. Measurement of serum HBcrAg was performed using a CLEIA Lumipulse G1200 automated analyzer (Fujirebio Inc., Tokyo, Japan) and the reagents were provided by Fujirebio Inc., lot number: SAX5031 (Japan), with a lower limit of detection of 2.0 log U/mL, and a linear range of 3.0 log U/mL-7.0 log U/mL.



Results: Median age was 42 years old. Eighteen patients were male. Mean ALT was 35 U/ml, Mean HBV DNA level and HBcrAg level were 2.85 log IU/mL, and 3.7 log U/mL. HBcrAg level exhibited high degree of correlation with HBV DNA ($r = 0.512$, $p = 0.006$). (Figure 1)
Conclusions: HBcrAg titer exhibited distinct correlative profile with HBV DNA level in patients with CHB during antiviral therapy. It has a considerable utility in monitoring during antiviral therapy.
Keywords: Chronic Hepatitis B, HBV DNA, HBcrAg

PE-065

Determination of Liver Fibrosis Stage by Fib-4 in Patients with Chronic Viral Hepatitis

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Aims: There from in last year's hepatocellular carcinoma is most common malignancy, first of all cancers in Mongolia. Liver fibrosis leading to portal hypertension, and it can increase risk of hepatocellular carcinoma. Liver fibrosis is the accumulation of extracellular matrix in response to acute or chronic liver injury. Measurement of fibrosis helps to stage the severity of disease, it allows serial determination of disease progression and may play an important role in clinical management and determine patients prognosis. The aim of this study is to determine liver fibrosis stage by non-invasive serum biomarker FIB-4 in patients with chronic viral hepatitis.

Methods: 130 cases by chronic viral hepatitis at third central hospital in Mongolia from retrospectively reviewed and analyzed. The clinical data including AST, ALT and platelet count were recorded. FIB-4 was calculated.

Results: From all, males 47% and females 53%, with mean age of 49.72±14.3.All of the causes are HCV 63.85%, HBV 32.31%, HCV+HBV co-infection 3.85%.In cases of mean value of platelet count, ALT, AST was 211.18±72.9, 112.5±162.4, 82.37±101.5, respectively. FIB-4 was detected <1.45 cutoff value 48.46% non-fibrosis (F0 to F1 by Metavir), 1.45-3.25 score 33.08% fibrosis (F2 to F3 by Metavir), >3.25 cutoff value (F4 by Metavir) 18.46% cirrhosis. 31 (37.34%), 11 (26.19%), 3 (20%) cases of fibrosis were determined in patients with HCV, HBV, HCV+HBV co-infection, respectively.

Conclusions: Recorded data ALT, AST of chronic viral hepatitis were detected112.5±162.4, 82.37±101.5 respectively. In patients with chronic viral hepatitis, HCV FIB-4 was determined fibrosis in 43, 31 cases, respectively.

Keywords: FIB4, Mongolia, Liver fibrosis, HCV

PE-066

HCV/HBV Co-Infection: Epidemiology, Clinical Characteristics, Viral Interactions and Mortality

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Aims: Because of the shared modes of transmission, HCV/HBV co-infection is not uncommon, especially in endemic areas and among subjects with a high risk of parenteral transmission. Patients with dual HCV/ HBV have a higher risk of progression to cirrhosis and decompensated liver disease with an increased risk of hepatocellular cancer (HCC). HCV/HBV co-infected patients represent a diverse group with various patterns of viral replication. The aim is to summarize the risk factors and epidemiology of HCV/HBV co-infection and to describe its clinical characteristics in two medical centers for period of 2012-2016.

Methods: In total 408 patients with chronic viral hepatitis C (HCV) with mean age of 52 (range 27-77) years were examined. HCV/HBV was diagnosed in 25 (6%) of them, 19 (80%) were men. In this study we prospectively assessed serological, virological, biochemical parameters and instrumental investigations. The mean MELD score was 22.6±3.2 (13-47).

Results: The prevalence of hepatitis B (HBV) co-infection in a total of 408 patients with chronic HCV was 6%. Injection drug use was the predominant risk factor for dual HCV/HBV (85%). Higher rate of liver cirrhosis (LC) 20 (80%) and decompensated liver disease (Child-Pugh class C 40%) were reported in co-infected patients. Two of them were diagnosed with chronic hepatitis, three with HCC. Male sex, previous alcohol abuse and older age (>60) were predictors for developing of HCC in co-infected cirrhotic patients. The following complications were revealed in patients with liver disease decompensation: ascites in - 10 (40%), Hepatic encephalopathy in 5(20%), variceal bleeding-in 4 (16%), Hepatorenal syndrome (HRS) – in 4(16%). The patients with combined HBV/ HCV showed the following spectrum of virological profiles: 18 (72%) of HBV/HCV co-infected patients appeared to have high replication of HCV and inactive HBV replication, 4 (16%) - high HBV DNA levels and undetectable HCV RNA, three others presented active replication of both HCV/ HBV. The overall mortality was 20%, the main causes of mortality were HE (30%) and HRS (25%).

Conclusions: HCV /HBV dual infection is a complex clinical/virological entity. Decompensated liver disease were reported in (40%) of coinfected patients. The HCV replication was higher in most of coinfected patients (72%). The mortality was associated with complications of HE and HRS. The correct assessment of HBV and HCV replication is mandatory for proper therapeutic approach.

Keywords: Co-infection, Epidmiology, HCV-RNA, Mongolia

HCV,Basic

PE-067

MicroRNA-99a Restricts Hepatitis C Virus Replication by Blocking mTORC1-Mediated de novo Lipogenesis

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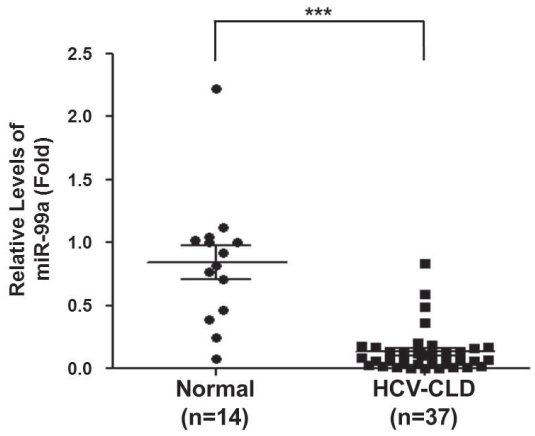
Aims: Lipid droplets are critical for the viral replication and packaging in the life cycle of hepatitis C virus (HCV). The mamma-

lian target of rapamycin (mTOR) signaling pathway is a major cellular pathway involved intracellular lipid droplet formation. In this study, we have demonstrated that miRNA-99a, a miRNA that has been reported to regulate mTOR pathway and cell survival, restricts hepatitis C virus replication by blocking mTORC1-mediated *de novo* lipogenesis.

Methods: Huh-7 cells were infected by cell culture-produced HCV (JFH-1; genotype 2a). HCVcc infected cells and full-genomic HCV replicon (FGR) cells were used for miRNA experiments. Immunocytochemistry was performed to quantify lipid droplets and HCV antigen after treatment of miRNA mimics or inhibitors. Serum samples of HCV-infected patients and those of age-matched healthy controls were collected and miR99a level was quantified by real-time qPCR.



Results: The relative expression of miR-99a was significantly lower in the sera of the patients with chronic HCV infection compared to the sera of those without viral hepatitis. HCVcc infection caused downregulation of miR-99a expression in Huh-7 cells, and FGR cells showed lower expression of miR-99a than wild-type Huh-7 cells. Forced expression of miR-99a-5p resulted in dramatic decrease in intracellular and secreted HCV RNA levels in HCVcc-infected cells. Using *in silico* analysis tools, mTOR was identified as a potential target of miR99a with a high binding score. HCVcc-infected Huh-7 cells showed increased expression of mTOR protein with increased phosphorylation of downstream targets that include the eIF4E binding proteins (4E-BP) and the ribosomal S6 kinase (S6K). Transfection of miR-99a-5p mimics resulted in the decreased level of mTOR protein and decreased phosphorylation of 4E-BP and S6K in FGR cells. The mRNA and protein level of sterol regulatory element binding protein-1c (SREBP-1c), the master transcriptional regulator of fatty acid and triglyceride synthesis, was decreased when either miR99a mimics or si-mTOR was transfected. Target genes of SREBP-1c were also downregulated at both mRNA and protein levels after transfection of miR99a mimics. In cells transfected with miR-99a-5p mimics, oleic acid-induced intracellular lipid accumulation were significantly decreased compared to cells treated with scrambled miRNAs. Forced expression of mTOR rescued the replication of HCV RNA and lipid droplet accumulation in miR99a mimics-transfected FGR cells, suggesting that mTOR is responsible for the anti-lipogenic activity of miR-99a.

Conclusions: Our data clearly demonstrate that miR-99a ameliorate intracellular lipid accumulation by regulating the expression of SREBP-1c and its target genes, and cause inefficient replication and packaging of intracellular HCV.

Keywords: Hepatitis C virus, MiR-99a, Lipid droplet, MTOR

PE-068

Change of Incidence of Hepatitis C Virus Infection after Transfusion by Introduction of Nucleic Acid Testing: A Big Data Analysis

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Aims: The risk of hepatitis C infection by transfusion is rated as RED level. About 0.2% of donors were positive for hepatitis C virus and the risk of infection due to transfusions is very high.

Methods: Using the National Health Insurance Service-National Sample Cohort database (million) from 2002 to 2013, we compared the incidence of hepatitis C after transfusion before and after Nucleic Acid Testing (NAT) was introduced. The study subjects were those who received blood transfusions from 2002 to 2012. Of these, persons diagnosed with hepatitis C from 2002 to 2003 were excluded. The final study subjects were observed until December 31, 2013.

Results: The final study subjects were 48518 persons. Of these, 72(0.14%) were diagnosed with hepatitis C infection after transfusion. The incidence density of HCV after transfusion of before the introduction in NAT was 4.3 per 10,000, and the incidence density of HCV after transfusion after introduction in NAT was 3.7 per 10,000. In the first year after transfusion, the incidence of HCV per 10,000 persons was 167.1 before the introduction of NAT and it decreased to 80.8 after the introduction of NAT. However, the incidence of HCV per 10,000 persons after the introduction of NAT is higher than annual HCV incidence of the general population as 18 persons (As of 2012 years).

Conclusions: The incidence density of HCV infection after transfusion per 10,000 people decreased after the introduction of NAT compared with before the introduction. However, constant attention is needed considering continuous infection. In a further study, the National Health Insurance claims data will be used to analyze the incidence of hepatitis C infection after transfusion.

Keywords: Nucleic acid testing (NAT), Transfusion, Incidence, Big data

HCV,Clinical

PE-069

Pharmacokinetics, Safety, and Efficacy of Glecaprevir/Pibrentasvir in Pediatric Patients with Genotypes 1-6 Chronic HCV Infection: Part 1 of the DORA Study

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Aims: The pangenotypic, direct-acting antivirals glecaprevir (GLE; identified by AbbVie and Enanta) and pibrentasvir (PIB), are coformulated (G/P) and approved to treat adults with chronic HCV infection. G/P achieved high SVR12 rates in Phase 2 and 3 studies, leading to an 8- and 12-week indication in HCV genotype (GT) 1–6 patients without cirrhosis or with compensated cirrhosis, respectively. An approved, pangenotypic pediatric HCV regimen is currently unavailable, and treatment options may include ribavirin (RBV); a pangenotypic regimen with improved tolerability for pediatric patients remains an unmet need.

Methods: DORA (NCT03067129) is an ongoing phase 2/3, non-randomized, open-label, multicenter study evaluating the pharmacokinetics (PK), safety, and efficacy of G/P in pediatric patients with chronic HCV infection. This analysis includes only Part 1 of the study, conducted in adolescent patients 12–17 years of age who received the adult formulation of G/P (300 mg/120 mg). Part 2 will be conducted in patients aged 3–11 years given a pediatric formulation of G/P. Patients without cirrhosis or with compensated cirrhosis were either treatment-naïve or experienced with interferon (IFN) with or without RBV, or sofosbuvir plus IFN with or without RBV. In Part 1, the adult formulation of G/P (300 mg/120 mg) was orally dosed once-daily with food for 8, 12 or 16 weeks. The primary efficacy endpoint was SVR12; the primary PK endpoint was steady-state AUC values for GLE and PIB. The secondary endpoints were C_{max} and clearance of GLE and PIB at treatment week 2, and on-treatment virologic failure, relapse, and reinfection. Adverse events and clinical laboratory abnormalities were monitored.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	G/P (N=47)
Male, n (%)	21 (45)
White race, n (%)	35 (74)
Age, median (range), years	14 (12–17)
Weight, median (range), kg	58 (32–109)
HCV genotype, n (%)*	
GT1	37 (79)
1a/1b subtype	24 (51) / 13 (28)
GT2	3 (6)
GT3	4 (9)
GT4	3 (6)
HCV RNA median (range), log_{10} IU/mL	6.2 (4.6–7.2)
Without cirrhosis, n (%)	47 (100)
HCV treatment-naïve, n (%)	36 (77)

*No patients with GT5 or GT6 infection were enrolled

Results: Part 1 enrolled 48 adolescent patients; 1 patient was never dosed and thus excluded from this analysis. Table 1 shows baseline demographics. Overall, 47/47 patients (100%) achieved SVR4; 34/34 (100%) patients with available data achieved SVR12. No on-treatment virologic failures or relapses have occurred to date. Intensive PK exposures of GLE and PIB were comparable to exposures in adults. The most common adverse events (AEs) were nasopharyngitis (26%) and upper respiratory tract infection (19%). No AEs led to treatment discontinuation, and no serious AEs occurred. No cases consistent with drug-induced liver injury were identified.

Conclusions: Adolescent patients with chronic HCV infection treated with G/P achieved high rates of SVR4, without incidence of virologic failure, serious AEs or treatment discontinuation. Final SVR12 and PK data will be presented at the meeting.

Keywords: Hepatitis C, Adolescent, Hepatitis

PE-070

Long-Term Hepatic and Extra-Hepatic Outcomes of CHC Patients Post Sofosbuvir-Based IFN-Free Treatment (LONGHEAD Study)-Interim Report

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Aims: Direct antiviral agents (DAA), sofosbuvir (SOF)/ledipasvir (LDV) and SOF plus ribavirin (RBV), have been proved to provide a sustained virological response (SVR) of ≥ 97% in treatment-naïve or treatment-experienced Taiwanese and Korean patients with HCV genotype 1 (HCV-1) and HCV-2 infection in prior two phase 3b clinical trials (NCT02021656, GS-US-337-0131 and NCT02021643, GS-US-334-0115). The aim of the study is to explore the long-term outcome of the SOF-based cohort who achieved SVR.

Methods: CHC patients receiving sofosbuvir-based DAAs in the parent studies are included for following up to 5 years. Their laboratory, image studies and clinical events in terms of liver non-liver related outcomes are prospectively documented.

Results: A total of 200 patients (Taiwanese patients: n = 104 from 10 sites, Korean patients: n = 96 from patients from 14 sites) are enrolled. The mean follow-up period is 10.4±4.4 months until Dec 2018. The mean age was 59.7 years, and male accounted for 39.5% of the population. Eighty eight (44%) of the patients were with hepatitis C virus genotype 1 (HCV-1) infection and received sofosbuvir /ledipasvir, whereas 112 (56%) HCV-2 patients received sofosbuvir/ribavirin. Twenty-Six (13.0%) patients had compensated liver cirrhosis, and 4 patients (2.0%) had HCC at LONGHEAD study enrollment. For the extra-hepatic manifestations, the proportion of hypertension, diabetes, dyslipidemia and history of acute myocardial infarction was 12.5%, 6.5%, 8.5% and 0.5%, respectively. Until 17 Dec, 2018, five patients withdrew study follow-up. There were 4 serious adverse events being reported (HCC [n = 2] and gastric cancer [n = 2]). At year 1, two patient developed new HCC. For extra-hepatic outcomes, four patients had newly onset diabetes and one patient had diagnosed dyslipidemia. None had cardiovascular event, and none had developed liver decompensation or mortality. Regarding the fibrotic evolution diagnosed by Fibroscan, the proportion of patients with improved, stationary and worsening fibrosis is 8.9%, 76.7% and 14.4% respectively. One hundred and fifty nine patients who achieved SVR12 had available virologic data 1 year after initiating LONGHEAD study. All of the subjects remain to have undetectable HCV RNA (HCV RNA < lower limit of quantification [12 IU/ml]). The SVR durability is 100% at year 1.

Conclusions: The short-term outcome in the SOF-based population is appreciated. Longer follow-up period is warranted to clarify the post-SVR benefits in the LONGHEAD cohort.

Keywords: HCV, DAA, SVR, Longterm

PE-071

An Open-Label, Randomized, Active Control Trial of 8 Versus 12 Weeks of Elbasvir/Grazoprevir for Treatment-Naïve Chronic Hepatitis C Genotype 1b Patients with Mild Fibrosis (EGALITE): Impact of Baseline Viral Loads and NS5A Resistance-Associated Substitut

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Aims: 12-week grazoprevir/elbasvir is highly effective in hepatitis C virus genotype 1 (HCV-1) infection. The efficacy of 8-week regimen for naïve patients with mild fibrosis is elusive.

Methods: HCV-1b naïve patients with mild fibrosis were randomized to receive 8 (n = 41) or 12 (n = 41) weeks of elbasvir/grazoprevir. The primary endpoint was SVR12 (HCV RNA < 12 IU/ml at post-treatment week-12).

Results: SVR12 was achieved by 87.8% (36/41) and 100% (41/41) in the full-analysis population and 90.0% (36/40) and 100% (41/41) in the per-protocol population in the 8-week and 12-week arms, respectively (all $P = 0.055$). In the 8-week arm, a significantly lower SVR12 rate was observed among patients with a high viral loads (HVL; > 1,500,000 IU/mL, 79% vs. 100%, $P = 0.042$) and those with baseline NS5A Y93H RAS > 15% (40.0% vs. 97.1%, $P = 0.004$). Between-group analysis demonstrated that patients with HVL and Y93H > 15% had a substantially lower SVR12 rate in the 8-week arm (40.0%) than the 12-week arm (100.0%). All four HCV-1b relapses had NS5A RAS Y93H > 99% at post-treatment week-12.

Conclusions: We confirmed that 12 weeks of grazoprevir/elbasvir is highly effective for HCV-1b naïve patients with mild fibrosis. A truncated 8-week grazoprevir/elbasvir regimen might be applied for those with low viral loads or without significant NS5A RAS.

Keywords: DAA, CHC, Grazoprevir, Elbasvir

PE-072

Decreased of Alpha-Fetoprotein Level among Patients with Liver Cirrhosis That Related to HCV Treated with Combination Therapy with Ledipasvir and Sofosbuvir

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Aims: Hepatocellular carcinoma (HCC) is considered one of the most lethal cancers, with most cases diagnosed at an advanced stage. The prevalence of HCC is high in Mongolia with men

116.6 cases and women 74.8 cases per 100,000 person-years. The hepatitis C virus (HCV) infection is one of the major causes of chronic hepatitis and hepatocellular carcinoma (HCC) in Mongolia. Viral infection with HCV can cause fluctuations in AFP that makes it difficult to differentiate between underlying liver disease and the development of HCC. The lack of specificity has limited the role of serum alpha-fetoprotein (AFP) for hepatocellular carcinoma (HCC) screening among patients with cirrhosis related to hepatitis C virus (HCV) infection.

Methods: Here we report 15 cases decreased of AFP level in patients with cirrhosis treated 24 weeks combination therapy with ledipasvir and sofosbuvir between 2017 to January 2019 were referred to the Liver Unit, Dornod Medical center Mongolia. All patients had been tested for blood chemistries, liver function markers, such as alanine aminotransferase (ALT), total bilirubin, prothrombin, an international normalized ratio (INR), creatinine, AFP and HCV-RNA.

Results: Of all patients, three were man and two were woman. The average age of the testimonies was 56 (between 44 and 68 years). Our patients had HCV genotype 1b and had HCV-RNA positive. The combination of the therapy with ledipasvir and sofosbuvir had significantly decreased the level of HCV-RNA from 3572350 to not detected ($P < 0.05$), ALT from 123.4 to 25.6 ($P < 0.05$), AFP from 43.8 to 17.8 ($P < 0.05$).

Conclusions: In conclusion, the combination of the therapy with ledipasvir and sofosbuvir is decreased AFP level and improved liver function tests in HCV related liver Cirrhosis of those patients.

Keywords: Alpha-fetoprotein, Ledipasvir and sofosbuvir

PE-073

Changing Cascade of Care for Hepatitis C in the Era of Direct-Acting Antivirals (DAAs)

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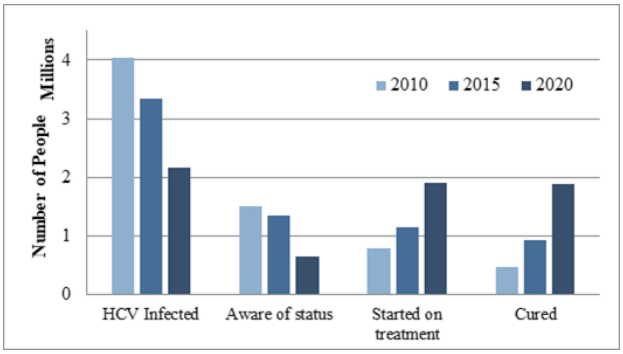
Aims: Our objective was to project changes in the cascade of care for HCV considering these factors.

Methods: We used a previously-validated mathematical model, Hepatitis C Disease Burden Simulation model (HEP-SIM), which projects the changing prevalence of HCV in National Health and Nutrition Examination Survey (NHANES) and non-NHANES population groups. HEP-SIM simulated the management of HCV from 2010 onwards, which included risk-based screening until 2013 and inclusion of birth-cohort screening afterwards; the rising HCV incidence resulting from new patterns of injection drug use; insurance expansion with the Affordable Care Act; and antiviral treatment options in different waves starting with peginterferon followed by the launch of first- and second-generation DAAs, including pan-genotypic drugs. Treatment efficacy was extracted from clinical studies and treatment rates based on insurance status and drug sales. We projected different steps of the HCV cascade of care for years 2010, 2015, and 2020.

Results: Our model estimated that in 2010, 4.0 million people had chronic viremia, and among those 1.5 million people (37.5%) were aware of their HCV infection status (Figure 1). In 2015, 3.35 million people were viremic and 1.35 million were aware of their status. Under current clinical practice, by 2020, 2.16 million are projected to remain viremic and 0.65 million (30%) aware of their infection. The number of people who achieved cure is projected to increase from 0.47 million in 2010 to 1.89 million in 2020.



Conclusions: Our model predicts that DAAs have substantially changed the HCV cascade, with a predicted increase in the HCV infected people expected to be cured by 2020. Despite this, under current screening/treatment, 1.89 million people will remain infected in 2020 with 70% of those unaware of their infection. Policies aimed at aggressive screening for HCV alongside controlling the rising HCV incidence could help further reduce the burden of HCV in the United States.

Keywords: HCV, Chronic hepatitis C, Cascade of care, Screening

PE-074

Ledipasvir/Sofosbuvir for 8, 12, or 24 Weeks Is Safe and Effective in Patients Undergoing Dialysis

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Aims: HCV treatments for patients on dialysis are associated with complexities including drug-drug interactions and risk of hepatotoxicity. Despite higher concentrations of the primary circulating sofosbuvir (SOF) metabolite in severe renal impairment, real-world case series demonstrated substantial use of SOF-based regimens in this population with no safety concerns identified. This study evaluated the safety, efficacy, and pharmacokinetics of ledipasvir (LDV)/SOF in patients with HCV infection on dialysis.
Methods: Patients undergoing hemodialysis or peritoneal dialysis were enrolled to receive LDV/SOF (90 mg /400 mg) fixed-dose combination once daily. Eligible patients had HCV genotype 1, 2, 4, 5, or 6 infection. Treatment-naïve patients without cirrhosis infected with genotype 1 received treatment for 8 weeks, patients with cirrhosis received treatment for 24 weeks, all other patients received 12 weeks of treatment. The primary efficacy endpoint was the SVR12 rate. The primary safety endpoint was the proportion of patients who discontinued therapy due to adverse events (AEs).
Results: 95 patients were enrolled in Taiwan, Italy, Germany, the USA, and Belgium. The median age was 61 years, 64% Asian, 22% interferon-experienced, and 20% had cirrhosis. Most patients had HCV genotype 1 (72%) or 2 (22%) infection. Treatment was well tolerated; there were no discontinuations due to AEs. To date, 87/95 (92%) of patients achieved SVR12; with no virologic failures. Two patients have not yet attended their post-treatment week 12 visit. Six patients died during therapy or the posttreatment period and none of the deaths were considered related to LDV/SOF. The most frequent AEs were muscle spasms and nasopharyngitis. SAEs occurred in 13%, none was assessed as related to LDV/SOF.
Conclusions: Treatment with LDV/SOF single tablet regimen in patients undergoing dialysis resulted in a 92% SVR12 rate with no virologic failures. The regimen was safe and well-tolerated with no treatment-related discontinuations or treatment-related SAEs.
Keywords: HCV, Dialysis, Ledipasvir, Sofosbuvir

PE-075

Safety and Effectiveness of HARVONI® (Ledipasvir/Sofosbuvir, LDV/SOF) from the 3rd Year Post-Marketing Surveillance (PMS) Data in Korea

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Aims: In Korea, LDV/SOF has been approved for the treatment of GT1/2/4/5/6 HCV infections in adults and adolescents aged 12 to <18 years. Marketing authorization holders in Korea are required to conduct PMS and submit annual safety reports to MFDS. This study analysed the results from the 3rd LDV/SOF PMS report.
Methods: In this open-label, non-interventional study, case report forms of 61 patients were collected from 13 institutions in Korea from 13th October 2017 to 12th October 2018. Of these, 60 were included for safety analysis; one was excluded due to violation of the usage. 53 out of the 60 patients were included in the effectiveness analysis; 7 with missing information were excluded.
Results: All the 60 patients included were GT1-infected; 53.3% were aged ≥65 years; 51.7% were male; 35% were treatment-experienced; 40.0% and 10.0% had compensated and decompensated cirrhosis, respectively. 80% had ≥1 comorbidity like history of cardiovascular disease, diabetes and HCC. 66.7% were on ≥1 co-medication and the most commonly used medications other than vitamin supplements were amlodipine, ursodeoxycholic acid and metformin. The mean total administration period of LDV/SOF was 11.85 weeks. The LDV/SOF+RBV group (n = 11) had more advanced liver diseases than the LDV/SOF group (n = 49). The rate of AEs was 43.3% and was higher in the LDV/SOF+RBV (81.8%) than the LDV/SOF (34.7%) groups. The rate of ADRs was 16.7% and was comparable between the two groups. The most common ADRs were fatigue, headache, and nausea (n = 2, respectively). 3 and 2 patients discontinued LDV/SOF and RBV due to AEs, respectively. LDV/SOF was effective across patient subgroups; 52 out of 53 achieved SVR.
Conclusions: The 3rd year PMS data demonstrated a good safety profile and high effectiveness in Korean patients without significant safety signals. More cases with further information on safety and effectiveness will be collected for subsequent reports.
Keywords: Harvoni, PMS, Ledipasvir, Korea

PE-076

A Case Report of Glecaprevir/pibrentasvir-induced Severe Hyperbilirubinemia in a Patient with Compensated Liver Cirrhosis

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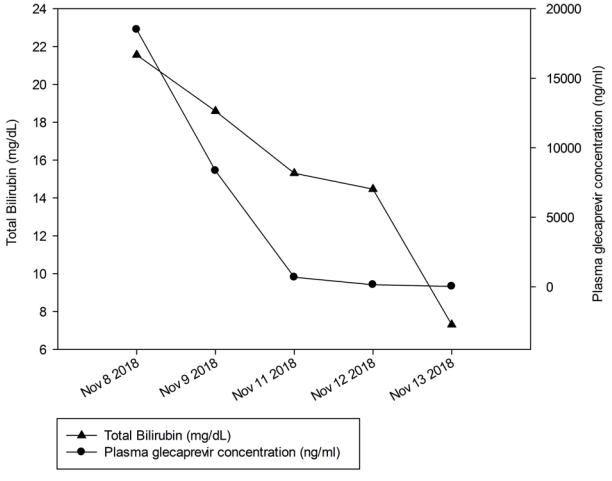
Aims: Glecaprevir/pibrentasvir, a pan-genotypic and ribavirin-free direct acting antiviral agent regimen, has shown significant efficacy and very few serious complications. However, as the drug metabolizes in the liver, it is not recommended in patients with decompensated liver cirrhosis. Herein, we report the case of a patient with compensated liver cirrhosis who developed severe jaundice after glecaprevir/pibrentasvir medication.

Methods: A 77-year-old man diagnosed with chronic hepatitis C-related compensated liver cirrhosis visited hospital due to severe jaundice after 12 weeks of glecaprevir/pibrentasvir medication.

Results: On the laboratory work-up, the total/direct bilirubin level was markedly elevated to 21.56/11.68 mg/dL from 1.81 mg/dL; the alanine aminotransferase and aspartate aminotransferase levels were within the normal range. We checked the plasma drug concentration level of glecaprevir, and 18,500 ng/mL was detected, which was more than 15 times higher than the drug concentration level verified in normal healthy adults. Glecaprevir/pibrentasvir was stopped and after 6 days, the drug concentration level decreased to 35 ng/mL and the serum total/direct bilirubin decreased to 7.49/4.06 mg/dL. Three months after drug cessation, the serum total bilirubin level normalized to 1.21 mg/dL and HCV RNA was not detected.

Conclusions: We report what is likely the first known case of severe jaundice after medication with glecaprevir/pibrentasvir in a patient with compensated liver cirrhosis. Clinicians should bear potential hyperbilirubinemia in mind when treating chronic hepatitis C with this regimen and should monitor the patient closely during follow-up laboratory exams, especially in elderly cirrhotic patients.



Keywords: Cirrhosis, Elderly, Glecaprevir, Hyperbilirubinemia, Hepatitis C virus

PE-077

Real Life Data of Daclatasvir and Asunaprevir Combination Therapy for Korean Patients Infected with HCV G1b without NS5A Resistance: Retrospective Multicenter Study

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Aims: Daclatasvir (DCV) and asunaprevir (ASV) combination therapy has shown a high viral efficacy for chronic genotype 1 (G1) hepatitis C virus (HCV) infected patients. This study was analyzed to the real life data for investigating the efficacy and safety of DCV and ASV combination therapy in Korean patients infected with HCV G1b without NS5A resistance.

Methods: A total of 349 chronic HCV genotype 1b patients treated with DCV and ASV who were enrolled and analyzed in a multicenter retrospective cohort.

Results: The study population was female dominant (n = 206, 59.3%) with 58.9 years. Thirty three percent (113/349) had cirrhosis and 28.8% (102/349) had previous history of HCV treatment at baseline. The median HCV RNA and ALT levels were 6.23 $\log_{10}$IU/mL and 64 IU/L, respectively. Among the total 349 Patients, 342 Patients (98.0%) were completed DCV and ASV combination therapy for 24 weeks. Only 7 patients had early discontinuation therapy (viral breakthrough; 2, adverse effect; 2 and patient request; 3). Rapid viral response rates (RVR) at week 4 were observed in 265 among 278 patients (95.3%). Sustained viral response (SVR) rates at post treatment week 12 were 98.8% (325/329). The viral response rates at the end of treatment were 97.7% (333/342). There was no significant dif-

ference of viral response between treat naïve group and treatment experienced group of HCV. (EVR 97.9% vs. 96.9%, *P* = 0.6) And the presence of cirrhosis also not affected to achieve the viral response. (EVR cirrhotic patients vs. non cirrhotic patients: 97.3% vs 97.8%, *P* = 0.8). There were no serious adverse events. The most common adverse events were fatigue and GI problem. Aminotransferase increases of greater than five times the ULN were observed in 3 patients.

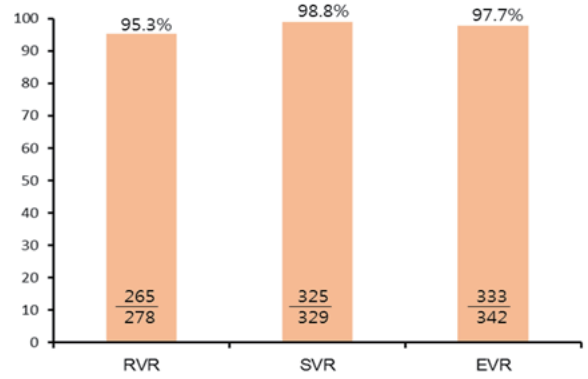

Figure 1.Virologic response rates in all population

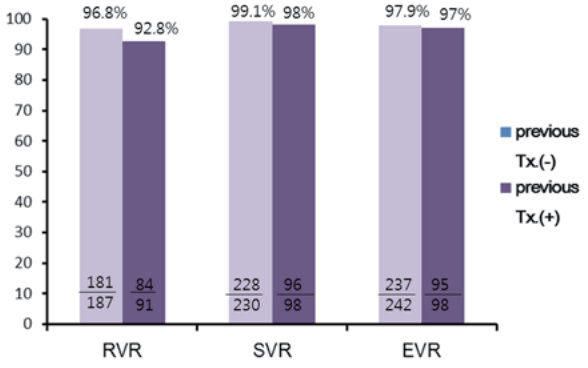

Figure 2. Virologic response rates in patients with/without previous history of treatment

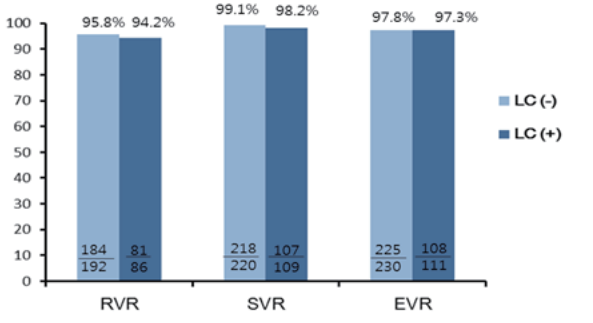

Figure 3. Virologic response rates in non-cirrhotic and cirrhotic patients

Conclusions: DCV and ASU combination therapy were well tolerated in Korean patients with HCV G1b infection without NS5A resistance and provided high SVR rates regardless of the experience of treatment and presence of cirrhosis.

Keywords: HCV, Genotype1b, Asunaprevir, Daclatasvir, Resistance associated variant

PE-078

The Efficacy and Safety of Glecaprevir and Pibrentasvir Treatment for Patients with Genotype 2 Hepatitis C Virus Infection in Real-World Experience: Interim Analysis of a Single Center

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Aims: Recently, various direct-acting antiviral (DAA) drugs is used to treat patients with hepatitis C virus (HCV) infection. An 8~12 week course of the combination of glecaprevir and pibrentasvir (Maviret®, AbbVie) is highly effective in patients with HCV infection, even in compensated liver cirrhosis. The purpose of this study is to find out the efficacy and safety profiles of Maviret® for the treatment in patients with genotype2 (GT2) HCV infection in real-world.

Methods: This study was performed on 49 adult patients diagnosed of GT2 HCV infection and treated with Maviret® at Hallym University Kangnam Sacred Heart Hospital from September 2018. Patients with HCV infection received Maviret® for 8 weeks, and cirrhotic patients received Maviret® for 12 weeks. Primary end point was sustained virological response after 12 weeks of treatment (SVR 12). The secondary end point was elevation of HCV RNA titer or occurrence of serious adverse events

Results: So far, a total of 49 patients with GT2 HCV infection were enrolled, 48 were identified as treatment naive patients and one was a treatment experienced patient. Of 49 patients, 35 patients finished treatment and all of them confirmed to ETR. 9 patients achieved SVR 12 and within in this period, no serious adverse events were found. 30 patients will be confirmed as having SVR 12 by June 2019. Headache and fatigue were reported as adverse events, but patients continue taking Maviret® because not observed other serious adverse events. Also, 1 patient was taking rosuvastatin and 4 patients were taking atorvastatin. Patients stopped taking rosuvastain and reduced the dosage of atorvastatin, due to concerning of adverse events but did not occurred during treatment. Of 11 patients had chronic alcoholics, 4 patients quit drinking, and 7 patients continued to drink but did not show any adverse events.

Conclusions: Although there were limited number of patients, we could find that the combination of glecaprevir and pibrentasvir (Maviret®) were effective and safe for the treatment of GT2 HCV infection in real-world experience. We suggest that Maviret® is the first treatment option for patients with GT2 HCV infection in Korea.

Keywords: HCV, Glecaprevir, Pibrentasvir

PE-079

Efficacy and Safety of Ledipasvir/Sofosbuvir for Treatment of Chronic Hepatitis C Patients

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Aims: Combination of ledipasvir (LDV)/sofosbuvir (SOF) has been approved in Mongolia for the treatment of genotype 1b hepatitis C virus (HCV) infected patients from 2016. We investigated virologic response and its clinical impact in CHC patients.
Methods: This retrospective study analyzed 830 patients with HCV infection who were treated with LDV/SOF from February 2016 to January 2019, were retrospectively enrolled from Dornod Medical center. Virologic response was measured at 4 weeks (rapid virologic response, RVR), at 12 weeks (end of treatment response, ETR), and at 12 weeks after the end of treatment (sustained virologic response, SVR12). Safety was assessed by review of adverse events, physical examinations, and laboratory findings.
Results: Of the 829 patients (male, n = 398 [48%] female n = 431 [52%] ; 100% were treatment naïve, HCV GT1b; mean age, 50.8 years; liver cirrhosis 207 [25%]), 622 patients (75.0%) were chronic hepatitis, mean ALT (76.9 IU/L), and mean HCV RNA level (3,464,490 IU/mL). In all patient, SVR12 was achieved in 824 (99.4%). Three patients early stopped the treatment due to headache problem and gastrointestinal troubles, therefore, they achieved SVR 12. During or after DAA treatment, hepatocellular carcinoma developed in 2 patients whose age was over 67 years.
Conclusions: Direct-acting antiviral (DAA) treatment of HCV GT1b infected Mongolian subjects resulted in a high rate of SVR. However, in some older patients, HCC can develop during or after DAAs treatment.
Keywords: Chronic hepatitis C, Direct-acting antiviral (DAA)

PE-080

Clinical Characteristics of Foreign Chronic Hepatitis C Patients in Daejeon-Chungcheong Area: Multi-Institutional Study

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Aims: The number of foreigners living in Korea has increased more recently than in the past, and the survey on chronic hepatitis C among foreigners is still almost nonexistent. The authors wanted to analyze foreign chronic hepatitis C patients who visited hospitals in Daejeon Chungcheng area to find out their clinical characteristics.
Methods: From January 2000 to December 2018, foreign chronic hepatitis C patients who visited six hospitals in the Daejeon Chungcheng area were analyzed. We used the number of the resident registration number which started with 5 for men and 6 for women in case of foreigners. In case of a North Korean defector, their resident registration number is same with that of Korean, so we recruited them by reviewing their chart.
Results: Total 217 patients were enrolled which is consisted of 90 male patients (41.5%) and 127 female patients (58.5%). Their mean age was 49.3 ± 12.6 (17-78 years). By country, China topped the list with 109 people (50.2%), followed by North Korea with 48 (22.1%), Mongolia with 18 (8.3%), Uzbekistan with 10 (4.6%) and Russia with 6 (2.8%). Since the first patient was registered in 2003, more than 10 patients have been registered since 2010, and more than 20 patients have been registered since 2013, every year. Genotype 2 (2-6 patients, 2a-89 patients, 2a/c-4 patients) were the most common with 99 patients (45.6%) and genotype 1(1a-7 patients, 1b-84 patients) was the second largest with 91 patients (41.9%). Genotype 3 was the third largest with 14 patients (6.5%), while genotype 6a was found in one patient (0.5%). Genotype 4, 5 was not found. Of the 217 patients, 154 patients (71.0%) received treatment. 84 patients (54.5%) treated with interferon agents (interferon-2 patients, peginterferon-82 patients) and 70 patients (45.5%) with DAA drugs. Sovaldi + ribavirin (29 patients) was used most, followed by daklinza + sunvepra (16 patients) and zepatier (16 patients). Viekirax + exviera, harvoni and maviret were used in three patients each. Of the 154 patients treated, 103 tested for SVR12 and 83 patients showed positive SVR12. Eighteen patients used interferon agents (interferon-1 patient, peginterferon-17 patients) and one each used daklinza + sunvepra and zepatier, respectively, for 20 patients who failed to achieve SVR12.
Conclusions: The number of foreign chronic hepatitis C patients has increased significantly compared to the past, especially since 2013. Unlike Korea, genotype 2 has more than genotype 1 and genotype 3 also takes up a certain portion, which requires publicity and education.
Keywords: Chronic hepatitis C, Foreigner, Genotype

PE-081

LDL-Cholesterol Level Was Elevated after Direct Acting Antivirals (DAAs) Administration in Genotype 2 HCV-Infected Patients: Real World Data from a Single Center Experience

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Aims: It was revealed that hepatitis C virus, especially genotype 3 HCV-infection, could promote hepatic steatosis and alter lipid metabolism. However, there was limited data regarding the

change of lipid profile after treating hepatitis C. Therefore, this study aims to show the change of serum LDL cholesterol level after the treatment of hepatitis C.

Methods: We retrospectively reviewed 258 patients who were treated with DAA for hepatitis C in a tertiary hospital. Among those, 58 patients, whose serum lipid profiles were measured at the time of DAA start and one year after DAA treatment, were selected. Serum LDL-cholesterol level was analyzed before and after the treatment in genotype 1b and genotype 2 HCV-infected patients.

Results: Of the enrolled 58 patients, the mean of age was 62.97(±11.00), the mean of serum RNA titer(IU/ml) was 2321532.89(±2349752.20); the number of patients in male and female was 23 (39.66%) and 35 (60.34%); the number of patients in genotype Ib and genotype 2 was 37(63.8%) and 21(36.2%), respectively. The mean of age in each group was 63.24 (±11.00) and 62.48 (±12.23),(P = 0.808). Overall, the mean of serum LDL-cholesterol before and after the treatment was 93.27 (±32.94) and 103.35 (P = 0.020). The mean of LDL-cholesterol before and after the DAA treatment in genotype Ib group was 94.76 (±33.94) and 101.40 (±34.58),(P = 0.239); the mean of LDL cholesterol before and after the DAA treatment in genotype 2 group was 90.64 (±31.73), 106.79(±28.61), respectively (P = 0.020). In multi-variable regression analysis, age, serum RNA titer, diabetes, hypertension, dyslipidemia, statin use, and types of DAA could not affect the serum LDL-cholesterol level after reaching the sustained virologic response.

Conclusions: Serum LDL-cholesterol level could be increased after the treatment of hepatitis C, especially in genotype 2 infection. Therefore, clinicians should monitor the lipid profile carefully after treating hepatitis C.

Keywords: Hepatitis C, Direct acting antivirals, Dyslipidemia

PE-082

Successful Treatment of Chronic Hepatitis C with a Combination of Glecaprevir and Pibrentasvir in a Patient Who Failed Previous Daclatasvir and Asunaprevir Treatment: A Case Report

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Aims: Chronic hepatitis C treatment is rapidly changing due to the introduction of direct antiviral agents (DAAs), and there are various attempts to re-treat hepatitis C infection using DAAs. We report a rare case that expected to achieve sustained viral response (SVR) with a combination of glecaprevir and pibrentasvir for four months in a patient who failed previous DAAs treatment with daclatasvir and asunaprevir.

Results: A 58-year-old woman came to the hospital for the elevated liver enzyme. Blood tests showed a white blood cell count of 4,550/mm^3, hemoglobin level of 13.1 g/dL, platelet count of 172,000/ul, aspartate aminotransferase of 217 IU/L, alanine aminotransferase of 97 IU/L, total protein of 8.4 g/dL, total albumin of 3.9 g/dL, prothrombin time of 79%, and total bilirubin of 1.0 mg/dL. The abdominal ultrasonography revealed a mild fatty liver. She had positive anti-HCV, HCV RNA level of 2,030,000 IU/ml, and genotype 1b. She had failed previous pegylated interferon and subsequent DAAs with daclatasvir and asunaprevir for 6 months. We treated her with a combination of glecaprevir and pibrentasvir. After one month, she experienced rapid viral decline and achieved undetectable levels of HCV RNA, however, the levels of aspartate aminotransferase and alanine aminotransferase were not normalized. At one month after a total of four months treatment, HCV RNA was not detected and liver enzymes were decreased, however not normalized. Nevertheless, we are expecting her to achieve SVR.

Conclusions: A combination of glecaprevir and pibrentasvir for four months might be a successful treatment option in a patient who failed previous DAAs treatment with daclatasvir and asunaprevir.

Keywords: Chronic hepatitis C, Sustained viral response, Glecaprevir, Pibrentasvir

PE-083

Prevalence and Geographical Distribution of HCV among Arkhangai Provinces in Mongolia

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Aims: Mongolia has a large burden of viral hepatitis, especially chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, which are associated with cancer and cirrhosis. In 2017, one of the central regions of Mongolia, Arkhangai province had the third highest HCV prevalence among the provinces in Mongolia. To define geographical distribution of HCV prevalence among the soums (administrative and geographical unit) of Arkhangai province.

Methods: All persons between the ages of 45 and 60 years old from the 19soums of Arkhangai were eligible for HCV antibody screening by a WHO prequalified rapid diagnostic testing (Cypress Diagnostica). The test results were collected by each of the soum'sphysicians and analyzed by SPSS-21 software by using relevant parametric and non-parametric tests.

Results: A total of 17,601 (81.1% of the eligible population) underwent screening, of which 3,289 (18.68%) were positive for hepatitis C antibodies. Most of screened population was female (9095, 52.0%), mainly herdsman (7206, 40.9%), married

(15425, 87.6%), educated to secondary level (11997, 68.2%) and aged 50-54 (9289, 52.8%).The prevalence varied by soums (range:11.1% in Jargalantsoumto24.9% in Erdenebulgansoum) and was associated with older age; the highest rate of HCV infection was among the 55-59 age group ($P < 0.001$), the median age of HCV seropositive individualswas 52±12.

Conclusions: HCV prevalence in Arkhangai is higher than the country average (16.7%). Our experience in Arkhangai, demonstrates that through commitment of provincial public health departments, massive screening of populations at risk forHCV infection is feasible in resource limited settings.

Keywords: HCV, Prevalance, Mongolia, Distribution

PE-084

Study of Alteration of Iron Metabolism in Chronic Hepatitis C in Mongolia

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Aims: Iron is pivotal for a number of fundamental metabolic process in cells. Liver plyas an important role in iron homeostasis by secreting a peptide hormone named hepciden. Liver injury, such as liver cirrhosis, alcoholic liver disease, and chronic hepatitis B and C leads to abnormal expression of hepcidin. The current study was aimed to determine the relationship between iron parameters in patients with chronic hepatitis C in Mongolia.

Methods: The current cross-sectional study investigated 20 randomly selected patients with HCV, registered at Mongolian National Center for Communicable Diseases. Serum iron and ferritin concentrations were determined by immunoassay. Hepcidin levels were analyzed using by ELISA according to the manufacturer's instructions.

Results: Compare with healthy subjects, relatively low level of hepcidin, high level of serum iron and ferritin were measured in patients with HCV. Depending on serum ferritin level, hepcidin value was measured differently in patients with HCV. Hepcidin value was strongly correlated either with ferritin (r=0.7, P = 0.002) and iron (r-0.5, P = 0.04).

Conclusions: Iron metabolism was disturbed in HCV, Serum ferritin and iron level was increased in patients with HCV. Hepcidin value was measured differently in patients with HCV depending on serum ferritin level.

Keywords: Iron, Metabolizm, HCV, Mongolia

PE-085

Direct Antiviral Agent (DAA) Treatment of Chronic Hepatitis C Results by APRI and FIB-4 Score in Mongolia

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Aims: Viral hepatitis infection is directly associated with the development of liver cancer.According to the WHO report, among patients with liver cancer in Mongolia, 46% have hepatitis C, 34% have hepatitis B and 14% have co-infection with more than one hepatitis virus. Novel DAA targeting hepatitis C virus (HCV) have revolutionized the treatment of chronic hepatitis C infection (CHC). We aimed to determine DAA treatment achievement among 40-65 years old Mongolians.

Methods: We examined the changes in fibrosis scores FIB-4 and APRI after DAA treatment of CHC.A total of 17,601 (81.1% of target group) underwent screening, of which 3,447 (19.5%) were positive for hepatitis C. 3049 of them were tested for HCV RHA. FIB-4 and APRI scores were calculated before and after treatment for each patients. The relevant parametric and nonparametric tests were used.

Results: In total 1778 or 58.3% of individuals who had viral load test had enrolled treatment, 60.7% of them was female, aged between 40-65 years old. 98.3% (1748) of individuals who tested by viral load test was undergone to DAA treatment.After DAA treatment 99.4% of them were achieved SVR12. Mean level of FIB-4 and APRI values significantly decreased from 1.48 (SD1.39) [CI95% 1.26-1.74] and 0.88 (SD1.68) [CI95%:0.56-1.32] to 1.05 (SD0.54) [CI95%:0.92-1.18] (P = 0.017) and 0.19 (SD0.17)[CI95%:0.15-0.23] (P = 0.001) respectively.

Conclusions: Patients with SVR after DAA therapy showed significant improvement on fibrosis scores FIB-4 and APRI. Also almost all of treated patients were achieved SVR12 which shows treatment was highly effective.

Keywords: DAA, Treatment, Hepatitis c, APRI

PE-086

SVR 12 Weeks after Therapy with Sofosbuvir/Ledipasvir Patients with HCV Genotype 1B: Real World Mongolian Experience

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Aims: According to the approval of the implementation of the National Prevention, Control and Elimination Program between 2016 and 2020 by Mongolian Government, treatment campaign started from January 2016. It can be concluded that as part of preliminary results of the National Program.Up to date, any information and preliminary results of the Program is not available. To assess efficacy and safety of LED/SOF in 5052 Mongolian patients infected with genotype 1 HCV, who received brand LED/SOF (Harvoni®) for 12 weeks within the framework of the Program.

Methods: In this prospective cohort study, treatment-naïve, cirrhotic and non-cirrhotic patients were treated with LED/SOF for 12 weeks; treatment-experienced patients were treated with LED/SOF for 24 weeks.The primary efficacy endpoint was sustained virologic response 12 weeks after treatment (SVR12) and occurrence of adverse events. Serum HCV RNA quantification was performed using a Roche COBAS®TaqMan.

Results: Among total of 5052 patients with HCV-genotype 1 infection, 5016 had successful viral eradication after 12 weeks or 24 weeks of antiviral therapy using LED/SOF, accounting for 99.3% of SVR12. During 12 weeks to 24 weeks antiviral therapy, the most common adverse event was headache 9.4% (473), fatigue 6.2% (312), abdominal discomfort 5.9% (296) and skin rash 2.8% (141).

Conclusions: LED/SOF combination therapyhas been shown to be highly effective and well-tolerated in our real-life study with high SVR rates.

Keywords: SVR12, SOF/LED, Genotype, Mongolia

PE-087

Risk Assessment Tool for HCV Screening in Mongolia

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Aims: Liver cancer is the most common cause of cancer related mortality in Mongolia (44%). Chronic hepatitis B and C infections are responsible for 95% of liver cancers in the country. To develop a standardized risk assessment tool for HCV infection to facilitate cost effective, case finding of chronic hepatitis C infection among the general population in the Arkhanghai Province of Mongolia.

Methods: A risk assessment survey was developed in Mongolian, including 31questions about behavioral and clinical factors relevant to acquisition of HCV infection. Statistical analysis was done using by SPSS-21.

Results: Of 17601 adults between ages of 40 and 65 who completed the assessment survey10524 (59.7%) individuals had > 4 risk factors. The age of individuals was the strongest predictor of HCV infection (age group 40-44 vs. 45-49 (OR = 3.26; CI95% 2.87-3.70), age group 40-44 vs. 50-54 (OR = 3.03; CI95% 2.67-3.45), age group 40-44 vs. 55-59 (OR = 2.45; CI95% 2.15-2.79) and age group 40-44 vs. >60 (OR = 1.39; CI95% 1.22-1.59). Other predictors included: gender (high among female) (OR = 1.45; CI95%, 1.34-1.58), having any kind of surgery in life time (OR = 1.42; CI95%, 1.302-1.55), history of blood transfusion (OR = 1.69; CI95% 1.48-1.94), bloodletting treatment (OR = 1.17; CI95%, 1.06-1.29), and tattoos (OR = 1.16; CI95% 1.05-1.29).

Conclusions: The tool can be used in resource limited settings to facilitate HCV positive case finding and screening promotion all around Mongolia. The tool is country specific and the strongest risk factor is the age and followed by risky behaviors for Mongolians.

Keywords: HCV, HCC, Screening, Mongolia

PE-088

Extended Virological Response after Sustained Virological Response in Patients with Sofosbuvir and Ribavirin Therapy

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Aims: Late relapse or reinfection were crucial issues after sustained virological response (SVR) in antiviral treatment for chronic hepatitis C. The persistence of SVR to direct antiviral agent therapy is unclear. The aim of this study was to investigate durability of virological response in patients with SVR after sofosbuvir and ribavirin (SOF-RBV) therapy.

Methods: We consecutively enrolled patients with chronic hepatitis C received SOF-RBV from September 2016 to November 2017. A SVR is an undetectable HCV RNA level after at 12 weeks of completing HCV therapy and extended virological response was defined as undetectable HCV RNA level after 24 weeks of SVR.

Results: Forty-four patients had genotype 2 chronic hepatitis C who completed SOF-RBV treatment and achieved SVR were enrolled. Median age was 60 (36 - 77) years and half of subject were male. Median baseline HCV RNA level was 5.94 (3.4 – 7.1) log IU/mL and median follow-up period was 53 (27 – 68) weeks after SVR. Serum HCV RNA was detected in 2 subjects at 31 and 54 weeks after achieving SVR. They were male and have

no history of prior interferon treatment. There was no evidence of cirrhosis on ultrasound and no dose-adjustment of ribavirin. Both subjects achieved end of treatment response, but rapid virological response was not shown (6.64 at baseline to 3.88 log IU/mL at week4) in one patient.

Conclusions: Most of patients with SVR after SOF-RBV treatment continue achievement of virological response. Assessment of extended virological response might be helpful to eradication of HCV infection.

Keywords: Hepatitis C, Antiviral treatment, Virological response

PE-089

Treatment Failure Rates of Direct-Acting Antiviral Agents for Chronic Hepatitis C: A Single-Center Study

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Aims: The aim of the present study is to investigate the failure rates of interferon (IFN)-free direct-acting antivirals (DAAs) when treating chronic hepatitis C virus (HCV) patients and to evaluate the factors associated with treatment failure, in a single center setting.

Methods: HCV patients who had previously been treated with IFN-free DAAs were retrospectively searched and enrolled. All patients had either genotype 1b or 2. Treatment success and failure rates and associated factors were analyzed in various DAAs. Treatment success was defined as achieving a sustained virologic response at 94 week (SVR 94) after the completion of the treatment. Treatment was considered as a failure when HCV ribonucleic acid (*RNA*) remained detectable during the treatment or became detectable again after the successful achievement of end-treatment virologic response.

Results: A total of 150 patients were enrolled in the study. Of them, 75 had genotype 1b and 75 had genotype 2. Among genotype 1b patients, 38 were treated with daclatasvir/asunaprevir (DCV/ASV), 21 were treated with elbasvir/grazoprevir (EBR/GZR), 9 were treated with ledipasvir/sofosbuvir (LDV/SOF) with or without ribavirin, 5 were treated with glecaprevir/pibrentasvir (G/P), and 2 were treated with ombitasvir/paritaprevir/ritonavir + dasabuvir (PrOD). Treatment success rates were 84.2%, 95.2%, 100%, 100%, and 100%, respectively. Among genotype 2 patients, 62 were treated with sofosbuvir/ribavirin (SOF/RBV), and 13 were treated with G/P. Success rates were 96.8% and 100%, respectively. DCV/ASV showed the success rate below 90%. Genotype 1b and initial HCV RNA level above 1,000,000 IU/mL were associated with reduced responsiveness.

Conclusions: Overall, in concordance with previous studies, our results demonstrate that DAAs are very powerful medications in eliminating HCV RNA. However, DCV/ASV showed suboptimal efficacy. Despite the proven effectiveness of DAAs, treatment failures do exist, so follow-up monitoring is mandatory. Current DAAs-resistant HCV mutants can arise anytime so development of new anti-HCV drug is still needed.

Table 1. Treatment success and failure rates in different DAAs in patients with HCV genotype 1b and 2

	Mutation	DAAs	Success (%)	Failure (%)
Total HCV patients treated with DAAs (n=150)	Genotype 1b (n=75)	DCV/ASV (n=38)	84.2	15.8
		EBR/GZR (n=21)	95.2	4.8
		LDV/SOF (n=9)	100	0
		G/P (n=5)	100	0
		PrOD (n=2)	100	0
	Genotype 2 (n=75)	SOF/RBV (n=62)	96.8	3.2
		G/P (n=13)	100	0

DAA, direct-acting antivirals; HCV, hepatitis C virus; DCV/ASV, daclatasvir/asunaprevir; EBR/GZR, elbasvir/grazoprevir; LDV/SOF, with ledipasvir/sofosbuvir; G/P, glecaprevir/pibrentasvir; PrOD, ombitasvir/paritaprevir/ritonavir + dasabuvir; SOF/RBV, sofosbuvir/ribavirin

Table 2. Baseline characteristics of patients with failed DAAs treatment

Patient No.	Sex	Age	Genotype	Mutation	Previous interferon treatment	LC	HCC	DM	BMI >30	Cancer	Poor compliance	Initial HCV RNA (IU/mL)	DAA	Treatment duration (week)	SVR 12	SVR 24	SVR 48	Second-line DAA	Result of Second-line DAA
1	M	60	1b	None	Not done	No	No	No	No	No	No	1,990,000	DCV/ASV	24	Yes	No		LDV/SOF+R	SVR 48
2	F	43	1b	None	Failed	No	No	No	No	No	No	4,860,000	DCV/ASV	24	No			None	N/A
3	M	46	1b	None	Not done	No	No	No	No	Lymphoma	No	1,150,000	DCV/ASV	24	Yes	Yes	No	None	N/A
4	F	55	1b	L31V, Y93H	Not done	Yes	No	No	No	No	No	3,500,000	DCV/ASV	24	No			LDV/SOF+R	SVR 72
5	M	66	1b	None	Not done	No	No	No	No	No	No	4,720,000	DCV/ASV	relapsed at 10				None	N/A
6	F	57	1b	L31V, Y93H	Failed	No	No	No	No	No	No	1,490,000	DCV/ASV	relapsed at 12				LDV/SOF+R	failed
7	F	47	1b	None	Not done	No	No	No	No	No	Yes	2,200,000	G/P	12	Yes	No		None	N/A
8	F	80	2a	None	Not done	No	Yes	No	No	No	No	1,640,000	SOF/RBV	12	No			None	N/A
9	M	59	2a	None	Not done	No	No	No	No	No	No	7,350,000	SOF/RBV	12	Yes	No		G/P	SVR 24

M, male; F, female; LC, liver cirrhosis; HCC, hepatocellular carcinoma; DM, diabetes mellitus; BMI, body mass index; HCV, hepatitis C virus; DAA, direct-acting antivirals; DCV/ASV, daclatasvir/asunaprevir; EBR/GZR, elbasvir/grazoprevir; LDV/SOF, with ledipasvir/sofosbuvir; G/P, glecaprevir/pibrentasvir; PrOD, ombitasvir/paritaprevir/ritonavir + dasabuvir; SOF/RBV, sofosbuvir/ribavirin; SVR, sustained virologic response; N/A, Not available

Keywords: Direct-acting antiviral, Hepatitis C virus, Treatment failure

PE-090

Direct-Acting Antivirals about Diminishment of Liver Fibrosis after Chronic Hepatitis C Treatment

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Aims: Direct-acting antivirals (DAAs) are known to eradicate chronic hepatitis C (CHC) virus infection, and prevent progression of liver fibrosis. Liver fibrosis may predispose to liver cirrhosis or hepatocellular carcinoma, but regression of fibrosis was not evaluated well in real world. Therefore, assessment of liver fibrosis in patients with CHC can predict the prognosis after treatment. We investigated the effect of DAAs on liver fibrosis by non-invasive methods like elastography and serum biomarkers and evaluate the correlations of these methods.

Methods: We retrospectively analyzed CHC patients who were treated with DAA and reached SVR12 from January 2016 to

October 2018. The degree of liver fibrosis was assessed using serum biomarkers such as APRI and FIB-4. The APRI was calculated as AST level/ (Upper limit of normal AST)/platelet counts (10^9/L) × 100, and the FIB-4 index was calculated as AST (IU/L) × age (years)/ [platelet count (10^9/L) × ALT (IU/L)$^{1/2}$]. Liver stiffness was assessed by two-dimensional shear wave elastography (2D-SWE). Pre and post-treatment serum biomarkers of fibrosis and SWE were evaluated and compared.

Results: A total of 68 patients with CHC were enrolled and treated by DAAs. The mean age was 58 years (52.3-73) and 31 patients (45.6%) were male. 18 patients 26.4%) with compensated cirrhosis were included. 48 patients (70.6%) had genotype 1B and 18 patients (226.4%) had genotype 2. After treatment with DAAs, APRI were decreased from 0.701 (0.391-1.705) to 0.328 (0.208-0.497, $P < 0.0001$), and FIB-4 were also decreased from 2.355 (1.436-5.095) to 1.860 (1.267-3.391, $P < 0.0001$). The median kPa of 2D-SWE were changed significantly from 6.85 (5.63-11.45) to 5.66 (4.83-7.43, $P = 0.013$). APRI and FIB-4 were correlated statistically significant before and after Treatment with DAA, but correlation between serum biomarkers and 2D-SWE were partially significant.

Conclusions: After treatment of CHC by DAAs, noninvasive fibrosis panels and 2D-SWE were shown to be improved. Treatment with DAAs may help the recovery of liver fibrosis but further study including larger number of patients should be done to compare the efficiency of each method.

Keywords: Direct-acting antivirals, Hepatitis C, Fibrosis, Elastograohy

PE-091

Non-Invasive Test for Estimation of Liver Fibrosis

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Aims: In 2015 the digestive disorders were the second leading cause of morbidity among Mongolian population. The observed mortality from cancer in 2013 was 23.4% including liver cancer which is the first most common cause of cancer death. Furthermore, the digestive disease related death accounts for 4.7% of all mortality. Recently many noninvasive markers for assessing liver fibrosis have been developed, and they are frequently used in clinical practice. FIB4 index had a predictive value to confirm the existence of significant fibrosis with a specificity of 74% and a sensitivity of 70% and APRI score had a sensitivity of 89% and a specificity of 75%.

Methods: Cross sectional study was carried out. A total of 120 patients were enrolled in this study including 40 healthy individuals, 40 patients with chronic viral liver disease and 40 patients with alcoholic liver disease. Complete blood count (PLT), biochemistry (AST, ALT), abdominal ultrasonographywere performed. APRI, FIB-4 scores were calculated and compared with the results of the laboratory tests.

Results: A total of 120 patients were enrolled in this study; 40% of patients were males. Their mean age was 43.43±10.93 years. Liver fibrosis stages that are determined by APRI score: FO-1 mild fibrosis accounts for 54.3%, F2-3 moderate fibrosis 40.6%, F4-cirrhosis 11.5%; by FIB4 score: 62.8% was in F0-1, 20.3% was in F2-3, 11.5% was in F4stage among alcoholic liver disease group. In viral disease group liver fibrosis stages that were evaluated by APRI score were 36.2%-F0-1 mild fibrosis, 32.4%-F2-3 moderate fibrosis, 31.4%-F4 severe fibrosis. Statistically significant difference were observed between alcoholic liver disease and viral liver disease groups in liver fibrosis stages that was determined with APRI score ($P < 0.05$). In the abdominal ultrasonography increased echogenicity in alcohol group 32.5%, in virus group 52,5%, hepatomegaly in alcohol group 43.6%, vena portae dilated in alcohol group 8.3%, in virus group 10.6%, splenomegaly in alcohol group 14.1%, in virus group 20.1%, splenic vein dilated on alcohol group 20.3%, in virus group 14.75%. Alcohol and viral hepatitis abdominal ultrasonography is a statistically significant difference. In the present study, we found a statistically significant negative correlation between FIB4 score and platelet count, moderate negative correlation between FIB4 score, and albumin, total protein level, weak correlation between alkaline phosphatase, GGT, total bilirubin levels and FIB4 score ($P < 0.05$). APRI correlated significantly with AST and ALT levels, whereas platelet count, total protein albumin levels demonstrated moderate negative correlation with APRI scores ($P < 0.05$).

Conclusions: The APRI F2-3, the FIB4 F0-1 and F4 scores showed high sensitivity for the diagnosis of alcohol related liver fibrosis. The FIB4 F2-3, F4 score showed high sensitivity for the diagnosis of virus related liver fibrosis. These measures also demonstrated significant correlation with the stage of liver fibrosis in patients with viral hepatitis. For non-invasive diagnosis of liver fibrosis F2-3, using FIB4 was related to necroinflammation, F4 was related with necroinflammation, cholestasis, hypersplenism, liver failure syndromes.

Keywords: APRI, Mongolia, Non-invasive, Fbrosis

PE-092

Treatment Effectiveness of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B among Mongolian Patients

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Aims: Mongolia has one of the highest rates of viral hepatitis in the world, leading to the highest rate of liver cancer (HCC) in the world. We followed and evaluated treatment outcome of patients with chronic hepatitis B, initiating their TDF regimen in Happy Veritas Clinic and Diagnostic Center.

Methods: Only the data of the first 18-months of treatment

were considered. A total of 399 patients (218 males and 181 females; age range, 17-81 years; average age, 42 ± 11 years) enrolled in the present study. The assessment of response to treatment after a year was performed using available data relating to viral load, quantitative HBV-DNA, qHBsAg, ALT and Transient Elastography (TE).

Results: According to inclusion and exclusion criteria, a total of 399 patients (218 males and 181 females) enrolled in the present study. The age range of the patients was 17-81 years. The ALT level range of the patients before treatment was 10-392 IU/l, with an average level of 47 (29; 88) IU/l. Among the 399 patients 176 had ALT levels of < 40 IU/l and 223 had an ALT levels of > 41 IU/l. After 18 months the range of ALT level of the patients was from 12 to 160 IU/l, with an average level of 36 (26; 57) IU/l and 231 patients had ALT levels up to 40 IU/l, 168 patients had an ALT levels more than 41 IU/l. The distribution of patients in different fibrosis stages was: FO - 40% (n = 85), F1 – 9% (n = 19), F2 – 23% (n = 48), F3 – 18% (n = 39), F4 – 21% (n = 21). By month 12,71% of the patients with available data (n = 175) had HBV-DNA <30 IU/mL, 25% were decreasing and 3% were increased HBV-DNA quantity. Mean HBsAg quantity was increased from 2409 to 3253 IU/mL.

Conclusions: Treatment of HBV using TDF in Mongolia is started only few years ago. TDF shows significant antiviral activity against HBV. But quantity of HBsAg was increased. And ALT level was increased in 12 months and decreased in 18 months. Therefore, we need to study deep to understand the reason of elevation of ALT and HBsAg quantity. For patients who had fibrosis stage lower than F2 after treatment TE result decreased. And for patients who had a higher fibrosis stage (up to F3 stage) liver stiffness has increased.

Keywords: TDF, HBV, DNA, Mongolia

PE-093

HCV Treatment after Curative Liver Resection or RFA in Hepatocellular Carcinoma Patients in Mongolia

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Aims: It's reported that stage of liver cirrhosis, macro and micro vascular invasion, portal vein tumor thrombus and cancer stage are associated with the postoperative recurrence of hepatocellular carcinoma (HCC). In this study we aimed to investigate theanti hepatitis C virus (HCV) treatment impact on the recurrence of HCC (Hepatocellular carcinoma) after curative resection or RFA (radiofrequency ablation) treatment.

Methods: Patients with active HCV related HCC who had undergone curative hepatectomyor RFA were enrolled and analyzed to clarify the significance of anti HCV treatment at National Cancer Center of Mongolia. All patients were preoperative and postoperative HCV-RNA level of higher than 1000 IU/mL.

Results: The recurrence rate in patients who had received anti HCV treatment was significantly lower than in those without anti HCV treatment ($P = 0.02$).

Conclusions: The patients with HCV treatment after curative liver resection or RFA showed lower recurrence rate than without HCV treatment patients. Antiviral therapy is recommended, especially for patients who underwent curative hepatectomy for HCV to decrease the recurrence of HCC.

Keywords: HCV, RFA, Mongolia, HCC

PE-094

Comparision of Methods That Evaluate the Prognosis of Liver Cirrhosis

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Aims: To compare the new method that evaluate prognosis of liver failure with the traditional method.

Methods: The 23rd October 2016 our study was proved by meeting of biochemical principles (notary in 47) in HSUM. 322 patients with liver cirrhosis who had been in department of gastroenterology of the Third State central hospital were evaluated. Before treatment we took the sample of hematology, biochemistry and coagulation. Laboratory examination performed by Sysmex-KX 21, Biochemistry by Humalizer 2000, for the coagulation we used Humaclot apparatus. All statistical analysis were conducted with the SPSS 19.0.

Results: Among all cases 39.34% of patients were in group A, 50.82% in group B, 9.84% in group C according to the Child Pugh classification. For the MELD score 10.93% of patients were in up to 10 score, 73.22% were in 10-19, 13.66% were in 20-29, 2.19% were in 30-39 score and there was no patients who had over 40 score. In the MELD classification total bilirubin or liver functional test indicate jaundice, INR point to coagulation, creatinine shows renal function thus it is more sensitive than the Child Pugh. Therefore we have some idea other researchers. PLT was 119.2±6.25 in A group according to the Child Pugh whereas PLT was 132.31±16.74*109/l in 0-9 score group in the MELD, PLT% was 26.99±1.35 in A group and 26.74±2.29 in 0-9 score of MELD, prothrombin time was 17.37±0.39 in A group and 16.36±0.91 in 0-9 score of MELD. The splenic length was 12.15±0.21 in A group whereas 11.78±0.53 in 0-9 score of MELD. This shows MELD classification enable to make early diagnosis and evaluate the prognosis therefore appropriate other researchers. In 2001 (Kamath et al) according to MELD the death within 3 months happened 27% of patients from lower 20 score and 73% of patients from higher 20 score. In our investigation 13.66% of patients necessitate urgent liver transplantation.

Conclusions: Among all cases 39.34% of patients were in group A, 50.82% in B, 9.84% in C according to the Child Pugh clas-

sification. For the MELD 10.93% of patients were in up to 10 score, 73.22% were in 10-19, 13.66% were in 20-29, 2.19% were in 30-39 score and there was no patients who had over 40 score.

Keywords: Liver cirrhosis, Mongolia, MELD, HCV

Liver Cirrhosis, Portal Hypertension with Cx., Basic

PE-095

Human Adipose Derived Stem Cells Promote Liver Regeneration in Hepatic Fibrosis Model by Controlled Releasing Hepatocyte Growth Factor

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Aims: Although mesenchymal stem cells (MSCs) provide effective therapy for liver fibrosis, there are conflicting data regarding their marginal therapeutic effects. This study aimed to enhance the potential of hepatocyte regeneration in human adipose mesenchymal stem cells (ASCs) and investigate whether they have robust therapeutic efficacy in experimental liver fibrosis.

Methods: ASCs were cultured with four cytokines (ASC-C), the expression of hepatogenic factors was detected by microarray, and the effects of conditioned medium (CM) from ASC-C on the activation of hepatic stellate cells were analyzed. The therapeutic effects and mechanism of liver fibrosis induced by thioacetamide (TAA) were determined after cell transplantation. ASC-C exhibited high levels of hepatogenic (HGF, G-CSF), anti-apoptotic (IGFBP-2), and chemokine (IL-8) genes and increased expression of hepatocyte specific proteins.

Results: ASC-C CM inhibited the activation of hepatic stellate cells *in vitro*, and injection of ASC-C significantly delayed TAA-induced liver fibrosis and improved liver function and regeneration *in vivo*. In addition, human albumin-expressing ASC-C were observed in the livers of recipient animals. High levels of expression of HGF and its downstream signaling molecules, including p-38, were detected in the ASC-C-injected livers. Transplantation of ASC-C exerts anti-fibrotic effects and accelerates liver regeneration.

Conclusions: Thus, ASC-C may be a novel candidate for the enhanced treatment of liver cirrhosis in clinical settings.

Keywords: Stem cell, Fibrosis

PE-096

Novel Self Nano Emulsifying Formulation of Furosemide: A Drug Used in Portal Hypertension

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Aims: Poor water solubility is one of the reasons for erratic absorption after oral administration of furosemide (FSM), an antihypertensive loop diuretic. Aim of this study was to utilize Self nano emulsifying drug delivery system (SNEDDS), a novel drug delivery system, for improvement of water solubility, permeability and ultimately bioavailability of FSM.

Methods: FSM solubility was determined in various vehicles oils, surfactants and co-surfactants. Self-emulsification region for the rational design of SNEDDS formulations was identified by pseudoternary diagrams. Developed formulations were characterized by zeta potential determination, droplet size analysis, dilution test, viscosity determination, *in vitro* dissolution studies and *in vivo* pharmacodynamic evaluation.

Results: A remarkable increase in dissolution was observed for the optimized SNEDDS when compared with the plain FSM and marketed formulation by *in vitro* dissolution studies. The pharmacological effect of FSM was improved by SNEDDS formulation as compared to plain FSM.

Conclusions: The study confirmed that SNEDDS formulation can be used as a possible alternative to traditional oral formulations of FSM to improve its bioavailability.

Keywords: SNEDDS, Diuretic, Bioavailability, Dissolution

PE-097

The Expression of TSLP in Liver Fibrosis: Rat Bile Duct Ligation Model

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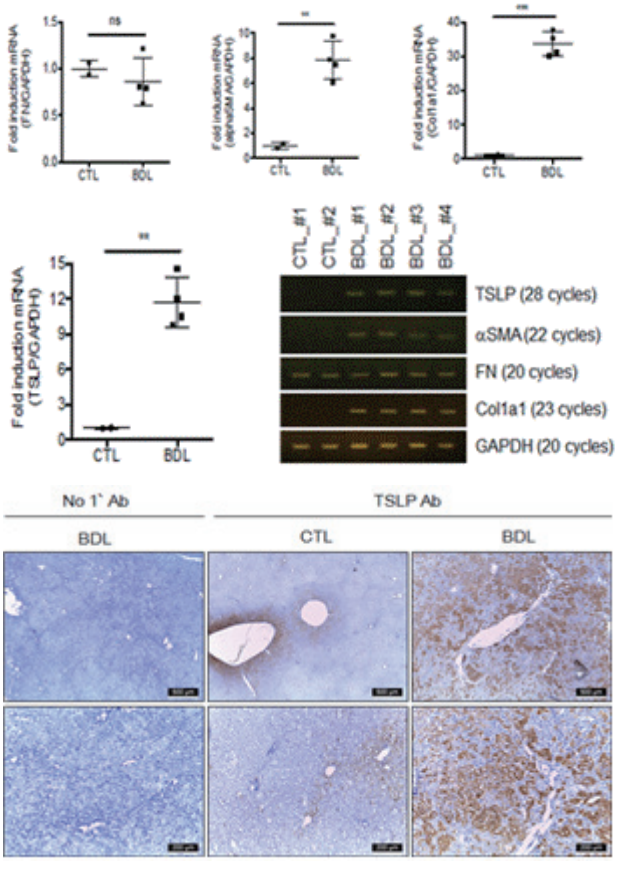
Aims: Thymic stromal lymphopoietin (TSLP) is cytokine expressed by epithelial cell and known as a mediator to regulate tissue inflammation and fibrosis. However, the role of TSLP in liver fibrosis in largely unknown. Recently, hepatocyte derived TSLP is detected in liver biopsies from chronic hepatitis C patients and it has effect to condition dendrite cells to drive CD4+ Th17 differentiation that is play a role in the progression of liver fibrosis. The extrahepatic bile duct ligation (BDL) is induced to cholestatic pattern liver inflammation and cirrhosis. This study is aimed to investigate the expression of TSLP on liver fibrosis in BDL rats.

Methods: We used male Sprague-Dawley rats with an initial body weight of 250-300g.Ten rats underwent BDL and five rats served as control. During the 4 weeks after BDL, blood was

withdrawn every one week to measure parameters (AST, ALT, ALP, albumin and total bilirubin) using rat tail vein. The progression of fibrosis was investigated by alpha smooth muscle anti-body (SMA), fibronectin, collagen Type I expression and specific immunohistochemistry (IHC) after scarifying the rat after 4 week of BDL. The expression of TSLP was evaluated by real time PCR, western blot and TLSP specific IHC in liver tissue.

Results: Biochemical parameters were consistently elevated during 4 weeks of BDL rats. To use hematoxylin eosin and Masson trichrome stain, we found increasing collagen density and proliferation of duct, stroma and fibroblast around portal area after BDL. The molecular markers for liver fibrosis were significantly increased in mRNA level attained by scarified BDL rat liver after 4 weeks compared with control one. This founding was paralleled by an increased overall expression of SMA, Fibronectin and collagen type I in western blot and a massive increased in fractions of theses positive cells in IHC in liver tissue from BDL rats. We observed the increase mRNA level of TSLP after 1weeks of BDL rat with increasing other fibrosis markers. And after 4 weeks of BDL, the mRNA level of TSLP and expression in western blot were significantly increased compared with control model. The positive fraction of TSLP specific IHC was also increased in liver tissue of BDL rats.



Conclusions: The TSLP expression was increased in cholestatic patterned liver inflammation and fibrosis. We can assume that TSLP is a cytokine that generally interact with the progress of liver fibrosis.

Keywords: Thymic stromal lymphopoietin, Cytokine, Liver fibrosis

PE-098

Enhanced Production of Steroid Drugs Intermediate Used in Treatment of Liver Cirrhosis

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Aims: Corticosteroids have been used to treat liver disorders and other autoimmune disease. Glucocorticosteroid is one example. Basically this drug reduces inlmaamtion caused by liver cirrhosis. This action is done by blocking signaling pathway of cell. Steroid drug forms a complex with receptor protein and bind with nuclear DNA. The production of this steroid drugs is done by lengthy chemical reactions. Androst-4-ene 3, 17 dione (AD) and hydroxyl derivative of AD are current precursors of corticosteroids. The present study was aimed at production of androstenedione by using microorganism.

Methods: For two different bioconversion reactions, two strains of *Mycobacterium species* were used. For production of AD, *Mycobacterium fortuitum* subsp. *fortuitum* NCIM 5239 and for 9 hydroxy-AD, *Mycobacterium* sp. NRRL B-8119 was used. Optimized medium B and nutrient broth were used as incubation medium. Analysis of products was done by quantitative thin layer chromatography.

Results: Ethanol and DMF exhibits enhanced biotransformation of AD after 144 h incubation time. But in case of hydroxylation, organic solvents suppressed the production of 9-hydroxy-AD. Vegetable oils in both bioconversion reactions showed nearly 90-95 mol% conversion of products. Sunflower oils exhibited nearly 88 and 92 mol% conversion of AD and 9-OH-AD respectively.

Conclusions: Production of AD and 9-OH-AD could be optimized for industrial production of corticosteroids. Organic solvents and oils may be used as substrate carriers to enhance industrial scale production of live failure drugs.

Keywords: Corticosteroids, Acute liver failure, Steroid drugs, L-asparaginase, Aspergillus niger

Liver Cirrhosis, Portal Hypertension with Cx., Clinical

PE-099

Helicobacter Pylori Infection in Patients with Liver Cirrhosis: Prevalence with Portal Hypertensive Gastropathy

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Aims: *Helicobacter pylori* infection has been recognized as one of the most common chronic bacterial infections in humans and is associated with peptic ulcer disease and gastric adenocarcinoma. The role of *Helicobacter pylori* (*H. pylori*) in the pathogenesis of portal hypertensive gastropathy (PHG) in cirrhotic patients is poorly defined. The aim of this study was to investigate the prevalence of *H. pylori* infection and its association with PHG in patients with liver cirrhosis.

Methods: We performed a retrospective study was conducted in the Internal Medicine Department, Dornod Medical center from 2017 to 2018. We examined the prevalence of *H. pylori* infection in 54 cirrhotic patients with PHG and using an anti-*H. pylori* IgG ELISA.

Results: Out of the 54 cirrhotic patients with PHG, men were 34, women were 20 mean age was 43 years. The presence of *H. pylori* was observed in 38 (72%) cirrhotic patients with PHG. Out of the 38 patients with PHG and *H. pylori* infection, 17 (44%) had severe PHG and 12 (31%) had mild PHG.

Conclusions: We concluded that *H. pylori* infection is a high prevalence of cirrhotic patients with PHG in Mongolia, which is may also be related to the severity of PHG.

Keywords: *Helicobacter pylori*, Portal hypertensive gastropathy, Liver cirrhosis

PE-100

Assessment of Liver Fibrosis and Cirrhosis by Fibroscan in Patients with Chronic Liver Disease

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Background: Liver biopsy is currently considered the gold standard for assessing hepatic fibrosis. However, it is an invasive procedure, with rare but potentially life-threatening complications. Fibroscan is a noninvasive imaging study for measuring liver stiffness by transducer probe-induced elastic share wave that propagates through liver tissue to measure its velocity.

Aims: To evaluate the accuracy of fibroscan in the assessment of liver fibrosis and cirrhosis in patients with chronic liver disease.

Methods: The present study was conducted on 61 patients with chronic liver disease. The study was conducted in Thai Nguyen Hospital from May 2017 to December 2018, and the disease was confirmed by standard diagnostic criteria. All cases were subjected to the following protocol: full history, clinical examination, laboratory investigation, ultrasound examination and liver biopsy. The patients were subjected to fibroscan examination and compared with liver biopsy. Fibrosis was evaluated according to the METAVIR system as validated for fibrosis. LS cut-offs were determined using receiver-operating characteristic (ROC) curves.

Results: There were 51 males and 10 females, and their ages ranged from 43 to 76 years, with mean age of 49 years. Liver stiffness was significantly correlated with liver fibrosis. To diagnose liver fibrosis: AUROC = 0.88 (95% CI = 0.86 - 0.98). At the cut-off level of 7.3 kPa, Sensitivity (Se), specificity (Sp), (positive predictive value) PPV and negative predictive value (NPV) were 81%; 92%, 91%; and 72% respectively. To diagnose cirrhosis: AUROC = 0.93 (95% CI = 0.86 - 0.99). At the cut-off level of 12.8 kPa, Sensitivity (Se), specificity (Sp), (positive predictive value) PPV and negative predictive value (NPV) were 85%; 91%, 90%; and 70% respectively.

Conclusions: Fibroscan is a promising noninvasive method for detection of liver fibrosis in patients with chronic liver disease. Therefore, fibroscan can be used regarding the decision of treatment and follow-up of patients with cirrhosis.

Keywords: Cut-off value, Fibroscan, Liver stiffness measurement, Fibrosis

PE-101

Intra & Extrahepatic Portosystemic Shunt Embolization Procedure in Two Patients with Recurrent Hepatic Encephalopathy

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Aims: Two different cases of intractable hepatic encephalopathy (HEP) with liver cirrhosis showed different pattern of portosystemic shunt, such as extrahepatic (paraumbilical collateral) & intrahepatic shunt. They had relatively good hepatic reserve function (CTP score ≤ 7), and other defined provocating factors were not noted. Two patients showed different clinical courses after shunt closure procedure using by vascular plug & coil insertion. We analized two different clinical course & predictive factor for treatment failure.

Methods: Two patients showed remarkable portosystemic shunts in abdominal CT scan and angiography. Ampulatz vascular plug & interlock coil were used for shunt closure via angiographic intervention procedure.

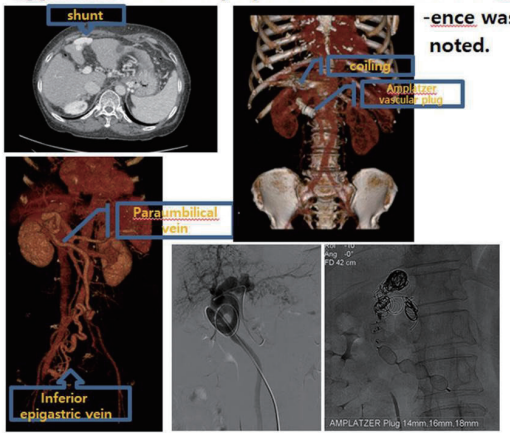
Results: Patient with extrahepatic shunt showed transiently aggrevated thrombocytopenia, hypotension and aggrevated ascites. They were improved by stopping propranolol and paracentesis. Later, ascites was easily controlled by diuretics. After procedure, she did'nt showed HEP. But patient with intrahepatic shunt showed unchanged hemodynamic change & ascites after procedure, and HEP with another intrahepatic portosystemic shunt was recurred at 4 weeks later after procedure.

Conclusions: Selective procedure of shunt embolization was somewhat useful in control of recurrent HEP. Transient hemodynamic change (suddenly decreased blood pressure, increased ascites & hypersplenism) was good predictor for effective HEP

management. At during or shortly-after intervention procedure, relapsed another portosystemic shunt made HEP recurrency.
Keywords: Encephalopathy, Portosystemic shunt, Cirrhosis

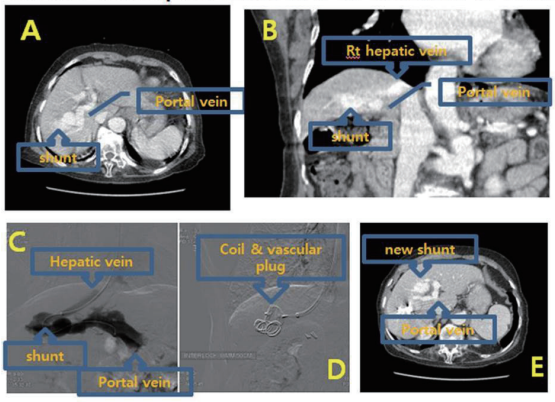
Case 1

Female (74 yr) showed recurrent HEP episodes (4 times within 2 months). Provocating factors (except hepatic shunt) were not seen. Transarterial portography showed large portosystemic shunt between left PV-paraumbilical vein-right inf. epigastric vein. After shunt embolization, she showed transiently hypotension, port area pain, aggrevated thrombocytopenia & ascites. But HEP recurr -ence was not noted.



Case 2

Female (83 yrs) showed recurrent HEP episodes (4 times within 5 months). Provocating factors (except intrahepatic shunt) were not seen. After shunt embo –lization, remarkable hemodynamic change was not seen. But after 1 months, she showed HEP sign and another intrahepatic shunt flow on abdomen CT scan.



A,B) CT scan showed intrahepatic shunt (PV~HV)
C,D) shunt embolization E) new intrahepatic shnt

PE-102

Low Serum Creatinine Level and Acute Kidney Injury Can Predict Long-Term Mortality in Cirrhotic Patients with Ascites

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Aims: Although renal dysfunction is a known prognostic factor in cirrhotic patients, serum creatinine is an inaccurate marker for glomerular filtration rate. We hypothesized that very low serum creatinine levels might be associated with other clinical factors besides renal function, and that acute kidney injury (AKI) could affect the long-term outcomes of cirrhotic patients with ascites.
Methods: We performed a retrospective study of hospitalized cirrhotic patients with ascites who were prescribed diuretics during hospitalization. The ability of baseline serum creatinine levels and changes in creatinine from baseline to predict all-cause mortaltity was analyzed. The absolute changes and percentage changes were calculated and AKI was defined by the Acute Kidney Injury Network classification.
Results: A total of 201 patients were included and 61 patients died during the mean follow-up of 35.8 ± 21.3 months. Baseline creatinine levels were lower but the absolute changes and percentage changes in creatinine were higher in non-survivors compared with survivors. The optimal cut off value to predict mortality was baseline creatinine of 0.5 mg/dL. Twenty-eight had low baseline serum creatinine (<0.5 mg/dL) on admission and AKI occurred in 23.9% of subjects. Multivariate analysis showed that a baseline serum creatinine<0.5 mg/dL on admission (hazard ratio: 2.58, 95% confidence interval 1.18-5.65, P = 0.014) and AKI (hazard ratio: 2.14, 95% confidence interval 1.16-3.94, P = 0.011) were significantly associated with long-term mortality.
Conclusions: Low baseline serum creatinine levels and AKI were independent predictors of all-cause mortality in hospitalized patients with cirrhosis and ascites.
Keywords: Creatinine, Acute kidney injury, Cirrhosis, Ascites

PE-103

Repeated versus Single Treatment of Esophageal Variceal Ligation after Esophageal Variceal Bleeding: Multicenter Retrospective Study

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Aims: International guidelines recommend repeated esophageal variceal ligation (EVL) for treatment of esophageal variceal bleeding. However, due to patient compliance and complications of repeated EVL procedure, many physicians perform single EVL treatment after varix bleeding. We aimed to compare the risk of variceal re-bleeding after repeated EVL versus single EVL.
Methods: This retrospective study included consecutive patients who underwent initial esophageal variceal ligation (EVL) for the

first esophageal variceal bleeding. Primary endpoint was the recurrence of variceal bleeding and uni-/multi-variate analyses were conducted to find independent predictors.

Results: A total of 210 patients were included: 133 in the repeated EVL group and 77 in the single EVL group. During follow-up duration (median = 46.5 months), 17 (12.8%) in the repeated EVL group and 36 (46.8%) in the single EVL group developed re-bleeding ($P < 0.01$ by log-rank test). However there were no difference of overall survival between the two groups ($P = 0.05$). Multivariate analysis showed that the single EVL group compared to the repeated group (adjusted hazard ratio [aHR] = 3.372, 95% confidence interval [CI] = 1.824–6.234, $P < 0.001$) was the only independent risk factor after adjustment for alcohol etiology (HR = 3.370, 95% CI = 1.717–6.618, $P < 0.001$), combined gastric varix (HR = 1.333, 95% CI = 1.250–9.612, $P = 0.017$) and high MELD score (HR=2.379; 95% CI = 1.192–4.748; $P = 0.014$).

Conclusions: Repeated EVL after esophageal varix bleeding can improve re-bleeding. However, there was no difference in overall survival. Further randomized control studies are needed.

Keywords: Esophageal variceal ligation, Esophageal varix, Bleeding, Recurrence

PE-104

Comparison of Gross Inspection by Surgeon or Pathologist, Ultrasonography, CT, MRI, Transient Elastography, APRI and FIB-4 for Prediction of Liver Cirrhosis

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Aims: Microscopic histopathologic confirmation is the gold standard for diagnosis of liver cirrhosis. Radiologic imaging, transient elastography (TE), and serum biomarker such as aspartate aminotransferase to platelet ratio index (APRI) and Fibrosis 4 (FIB-4) index are commonly used surrogates for prediction of cirrhosis. In addition, gross inspection by surgeon or pathologist can predict liver cirrhosis before microscopic histopathogic confirmation. The aim of this study is to compare these methods for prediction of liver cirrhosis.

Methods: From January 2015 to December 2017, we retrospectively reviewed patients with hepatocellular carcinoma who had been previously treated with hepatic resection or liver transplantation in the tertiary hospital. Radiologic imaging was assessed using ultrasonography, CT or MRI. APRI and FIB-4 were calculated by biochemical laboratory finding. Gross inspection by surgeon was based on operation record. Gross inspection by pathologist was based on gross findings of pathologic reports. Comparison of gross inspection by surgeon or pathologist, ultrasonography, CT, MRI, TE, APRI and FIB-4 were using the AUROC.

Results: Total of 205 patients were reviewed. Among them, three patients were excluded according to exclusion criteria. Finally, total of 202 patients were analyzed. Mean age was 57.7. Patients who were infected with hepatitis B virus were 153. One hundred patients were confirmed with microscopic histopathologic cirrhosis. Calculated AUROCs for prediction of cirrhosis were 0.685, 0.858, 0.768, 0.792, 0.792, 0.818, 0.756, and 0.759 respectively in gross inspection by surgeon and pathologist, ultrasonography, CT, MRI, TE, APRI and FIB-4. Gross inspection by pathologist was more effective than gross inspection by surgeon, APRI and FIB-4 ($P < 0.05$). Gross inspection by surgeon was less effective than gross inspection by pathologist, CT, MRI, TE and FIB-4 ($P < 0.05$).

Conclusions: According to the comparison of these methods, gross inspection by pathologist was the most effective method for prediction of cirrhosis.

Keywords: Cirrhosis, Pathology

PE-105

Clinical Spectrum of Precipitating Factors of Hepatic Encephalopathy in Cirrhosis of Liver: Experience in Western Part of Nepal

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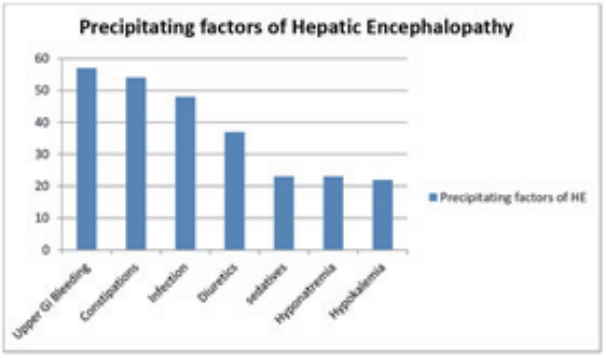
Aims: Hepatic encephalopathy is an extra hepatic complication of impaired liver function. It manifests as neuropsychiatric signs and symptoms associated with chronic liver disease in the absence of other neurological disorders. Its development leads a poor prognosis and it is associated with shortened patients' survival. Reversibility of the precipitating factors has prognostic significance. This study aims to ascertain the spectrum of precipitating factors of hepatic encephalopathy in patients with cirrhosis of liver.

Methods: This is a hospital based descriptive, cross sectional study. This study was conducted at Kaski Sewa Hospital and Research Center from 16th January 2018 to 28th January 2019. Total of117 cases of cirrhosis of liver who presented with hepatic encephalopathy and got admitted in ICU were included in the study. All patients of age more than 18 years, presenting with signs of hepatic encephalopathy were included and classified according to West Heaven criteria. Clinical data were recorded on a proforma and prognostic stratification through Child Pugh score.

Results: There were 70 (59.83%) male and 47 (40.17%) were female patients. Mean age of the patients was 56.45 (±11.261) years. Out of 117 patients, upper GI bleed (48.72%), constipation (46.15%), infection (41.02%) and electrolyte imbalance (34.12%) stood out as the most common precipitating factors. Usage of diuretics, sedatives, and excess dietary protein were

the other factors. More than one factor was found to be responsible in 54.7% of patients. Most patients were in grade IV (36.5%) and grade III (29.91%) of hepatic encephalopathy. Child Pugh class B (51.2%) and Class C (29.9%) were found. Mortality was 5.98%.



Precipitating factors	No. of patients (n=117)
Upper GI Bleeding	57
Constipation	54
Infection (WBC>11,000/cmm)/SBP	48
Diuretics	37
Sedatives	23
Hyponatremia(Sodium<135meq/L)	23
Hypokalemia (Potassium<3.5meq/L)	22

Conclusions: Upper GI bleed, constipation, infection, and electrolyte imbalance were the most common precipitating factors of Hepatic Encephalopathy in this study. Health education and awareness about these precipitating factors will help to decrease the incidence of hepatic encephalopathy in liver cirrhosis.

Keywords: Child Pugh score, Hepatic encephalopathy, Liver cirrhosis, Precipitating factors

PE-106

Comparison between Sandostatin Alone and Combined with Band Ligation for Hemostasis of Acute Variceal Bleeding

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Aims: Compare the efficacy of sandostatin alone and combination with endoscopic band ligation (EBL) to treat acute variceal bleeding.

Methods: 193 acute variceal bleeding patients were randomly chosen into study, divided into 2 groups: Group 1 (90 patients) treated by sandostatin alone, group 2 (103 patients) treated by sandostatin combined with endoscopic band ligation. Followed up for 4 weeks, compare the efficacy of hemostasis.

Results: Mean age group 1 is 48.8 ± 9.1, group 2 is 51.7 ± 9.6. Rate of Child-Pugh C in group 1 is 60.0%, in group 2 is 56.2%. Rate of severe bleeding in group 1 is 23.3%, group 2 is 10.7%. Size of EV F3 in group 1 is 56.7%, in group 2 is 73.8%. Number of 4-6 EVs in group 1 is 20%, in group 2 is 44.7%. Rate of rebleeding in group 1 is 33.3%, in group 2 is 13.6%; rate of free rebleeding in group 1 is 66.7%, in group 2 is 86.4%, $P = 0.001$. Rate of rebleeding within 5 days in group 1 is 23.3%, 0% in group 2, rate of rebleeding from 5 days to 2 weeks in group 1 is 3.3%, in group 2 is 1%; rate of rebleeding from 2 weeks to 4 weeks in group 1 is 6.7%, in group 2 is 12.6%, $P = 0.001$. Rate of mortality in group 1 is 20%, in group 2 is 5.8%, rate of success after treatment in group 1 is 80%, in group 2 is 94.2%, $P = 0.003$.

Conclusions: Combination of sandostatin and endoscopic band ligation has more efficacy than drug alone for hemostasis of acute variceal bleeding.

Keywords: Endoscopic band ligation, Acute variceal bleeding

PE-107

Relationship of Symptom-Onset-To-Hospital Arrival with Hospital Course in Patients with Variceal Bleeding

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Aims: Bleeding from varices in cirrhosis is a common complication with high mortality of liver cirrhosis. However, the relationship of symptom-onset-to-hospital arrival with hospital course in liver cirrhotic patients still remains incompletely understood.

Methods: In this study, 93 cases of admitted liver cirrhotic patients with variceal bleeding who underwent endoscopy at the emergency department from January 1, 2015, to December 31, 2017, were retrospectively analyzed and followed up. Patients were divided into 2 groups based on symptom-onset-to-hospital arrival time.

Results: In thirty-three patients (35.5%), the median interval between symptom onset and hospital arrival was 31.25 minutes. There was no significant difference in success rate of hemostasis, door-to-scope time, Child–Pugh scores, ICU admission and in hospital mortality. Logistic regression models showed that longer symptom-onset-to-hospital arrival was associated with increased in-hospital day (hospital day of 3.25 and 6.84 for symptom-to-hospital times of ≤60 min, and >60 min, respectively; $P < 0.05$).

Conclusions: In this result, symptom-onset-to-hospital arrival time affects to clinical course in variceal bleeding in cirrhotic patient. We suggest that the liver cirrhosis patient needs to be educated about complications and early hospital arrival after symptom onset.

Keywords: Liver cirrhosis, Endoscopy, Gastroesophageal varices

PE-108

Platelet Count Spleen Diameter Ratio to Predict Esophageal Varices in Patients with Liver Cirrhosis, in the Eastern Province Mongolia

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Aims: Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices is one of the major complications of portal hypertension. To validate whether the platelet count/spleen size ratio can be used to predict the presence of esophageal varices in Mongolian patients with hepatic cirrhosis.
Methods: This was a cross-sectional study to validate the diagnostic test for hepatic cirrhosis and was performed between 2017 to January 2019. Only stable patients were included in the study. Patients with active gastrointestinal bleeding at the time of admission were excluded. All patients underwent screening upper gastrointestinal endoscopy. Biochemical parameters were evaluated, and ultrasound was used to measure the longest diameter of the spleen. The platelet count/spleen diameter ratio was calculated and analyzed to determine whether it can predict the presence of esophageal varices.
Results: A total of 62 patients were included. The mean age was 56; 36 (58%) were men and 26 (42.0%) women. Child-Pugh classification, 35 (56%) patients were classified as class A, 23 (38%) as class B, and 4 (6%) as class C. The platelet count/spleen diameter ratio to detect esophageal varices independent of the grade showed using a cutoff value of ≤ 884.3, had 84% sensitivity, 72% specificity, and positive and negative predictive values of 93% and 41%, respectively.
Conclusions: The platelet count to spleen diameter ratio may be a useful tool for diagnosing EVs in liver cirrhosis noninvasively when endoscopy facilities are not available.
Keywords: Platelet count/spleen diameter ratio, Esophageal varices, Mongolian patients

PE-109

The Diameter of Eesophageal Varices Evaluated by Computed Tomography May Be an Important Predictor of Early Post-Endoscopic Variceal Ligation Bleeding

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Aims: Life-threatening bleeding following endoscopic variceal ligation (EVL) in cirrhotic patients rarely can occur. The present study aimed to evaluate the performance of computed tomography (CT) in predicting the risk of early post-EVL bleeding in cirrhotic patients.
Methods: We retrospectively investigated 285 cirrhotic patients who had undergone EVL. EVL was performed for prophylaxis or acute hemorrhage. The patients were classified into 2 groups: early bleeding (< 14days after EVL) and non-bleeding. We compared baseline characteristics including CT findings between the patient groups.
Results: Among the 285 patients treated with EVL, 232 were males and the average age was 61 years. 19 patients (6.7%) experienced early post-EVL bleeding and bleeding occurred 9.3 ± 3.5 days (range: 3-13 days). In univariate analysis ($P < 0.20$), total bilirubin ($P = 0.05$), prothrombin time ($P = 0.157$), presence of ascites ($P = 0.197$), and esophageal varix diameter on CT ($P = 0.005$) were significant predictive factors of early bleeding. In multivariate analysis, esophageal varix diameter on CT [OR 1.336, 95% CI (1.099–1.623)] was the only independent predictive factor of early bleeding.
Conclusions: A large esophageal varix diameter on CT is a risk factor for early post-EVL bleeding. Early identification of this high-risk group can provide a proper treatment strategies to improve patients outcome.
Keywords: Cirrhosis, Endoscopic variceal ligation, Bleeding, Computed tomography

PE-110

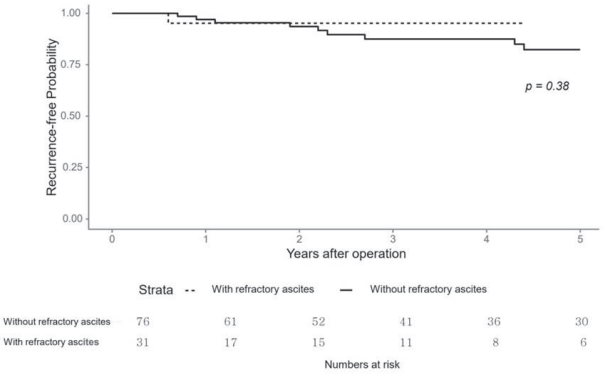
Prognosis of Surgical Hernia Repair in Cirrhotic Patients with Refractory Ascites

Sun Woong Kim[1], Minseok Albert Kim[1], Hee Jun Jang[1], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Kyu joo Park[2], Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute and [2]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

Aims: Abdominal wall hernias are common in patients with ascites. Elective surgical repair is recommended for the treatment of abdominal wall hernias. However, surgical hernia repair in cirrhotic patients with refractory ascites is controversial. In this study, we aimed to evaluate the outcomes of elective surgical hernia repair in patients with liver cirrhosis with and without refractory ascites.
Methods: From January 2005 to June 2018, we retrospectively reviewed the records of consecutive patients with liver cirrhosis who underwent a surgical hernia repair. Postoperative changes in liver function after surgery, recurrence and mortality rates within 30 days after surgery were evaluated.
Results: This study included 107 patients; 31 patients (29.0%) had refractory ascites. In those with refractory ascites, umbilical hernia was most common (83.9%), whereas incisional hernia was the most common type of hernia in patients without refractory ascites (46.1%). Preoperatively, cirrhotic patients with refractory ascites had a higher median model for end-stage liver disease (MELD) score (11.0 vs 13.0, $P = 0.001$) than those without refractory ascites. Among cirrhotic patients with refractory ascites, albumin ($P = 0.23$), bilirubin ($P = 0.37$), creatinine ($P = 0.97$), and sodium levels ($P = 0.35$) did not change significantly after surgery. The 30-day mortality rates (3.2% vs 0%, $P = 0.64$) and recurrence rates (hazard ratio, 0.410; 95% CI, 0.050–3.220; $P = 0.39$) were not differed significantly between cirrhotic patients with refractory ascites and cirrhotic patients without refractory ascites.
Conclusions: This study showed that mortality rate within 30

days, recurrence rate, and liver function did not differ by the presence or absence of refractory ascites. Surgical repair might be beneficial for treatment of hernia in all liver cirrhosis patients including patients with refractory ascites.



Keywords: Liver cirrhosis, Hernia

PE-111

The Impact of Liver Cirrhosis on the Mortality in Intensive Care Unit Patients

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Aims: The impact of liver cirrhosis on the mortality in intensive care unit (ICU) patients is not completely understood. Our purpose is to identify risk factors for mortality in ICU patients with liver cirrhosis.

Methods: We conducted a retrospective cohort study was based on research data of Taiwan's National Health Insurance that included patients with admission for intensive care between 1 January 2006 and 31 December 2012. We identified 1,250,300 patients aged 20 years and older with newly admission to intensive care unit and 37,197 of these had liver cirrhosis. With propensity score-matching for socioeconomic status, pre-existing medical conditions, and cirrhosis-related morbidities, 37,197 ICU patients without liver cirrhosis were selected for comparison. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of cirrhosis associated with 30-day, ICU, and one-year mortality were calculated.

Results: Compared with control, cirrhotic patients had higher 30-day mortality (aOR 1.60, 95% CI 1.53 to 1.68), particularly those with jaundice (aOR 2.23, 95% CI 2.03 to 2.45), ascites (aOR 2.32, 95% CI 2.19 to 2.46) or hepatic coma (aOR 2.21, 95% CI 2.07 to 2.36). Among ICU patients, liver cirrhosis was also associated with ICU mortality (aOR 144, 95% CI 1.38 to 1.51) and one-year mortality (aOR 1.40, 95% CI 1.35 to 1.46). Associations between cirrhosis of liver and increased 30-day mortality were significant in both sexes and every age group.

Conclusions: Liver cirrhosis was associated with 30-day mortality in ICU patients. Jaundice, ascites, hepatic coma, more than 4 admissions due to cirrhosis, and more than 30 days of hospital stay due to cirrhosis were exacerbated factors in cirrhotic ICU patients.

Keywords: Liver cirrhosis, Intensive care unit, Mortality

PE-112

Changing Trends in Epidemiology and Clinical Outcomes in Liver Cirrhosis in Korea: Eight Years Data in Single Center Study

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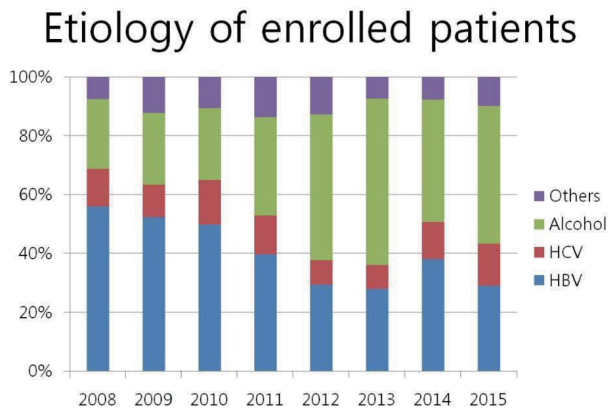
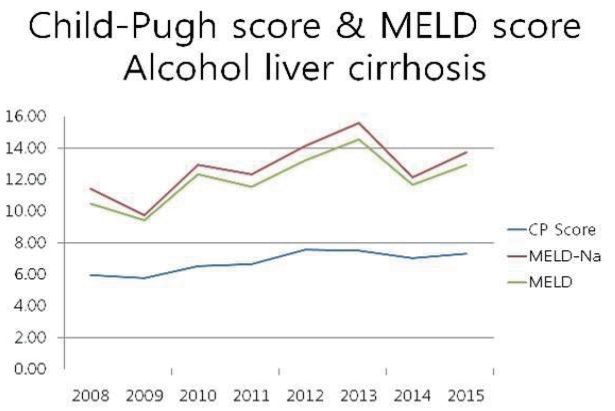
[1]Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Hospital and Medical School, Gwangju and Hwasun, Korea; [2]Department of Surgery, Chonnam National University Hospital and Medical School, Gwangju, Korea

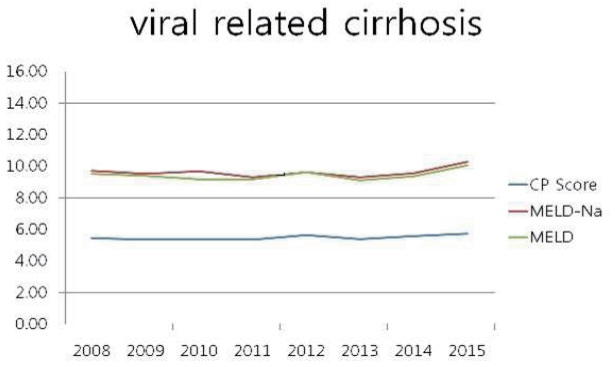
Aims: In Korea, the most common causes of liver cirrhosis are chronic hepatitis B, C and alcohol. However, recent study in Korea reported the prevalence of alcoholic cirrhosis continues to increase up to 31%, but steady decrease in the prevalence of HBV related cirrhosis. Therefore, nationwide survey of the current epidemiological status in Korean patients with liver cirrhosis is greatly needed.

Methods: This is a retrospective cohort study of consecutive cirrhotic patients (1,337 cases) who visited Chonnam National University Hospital from 2008 to 2015. Baseline characteristics (age, sex, etiologies and liver function), complication rates and mortality were also studied.

Results: This study included 1,337 cases of liver cirrhosis; 37.9% of which were due to hepatitis B (N = 507), followed by 37.9% due to alcohol (N = 480), and 11.6% due to hepatitis C (N = 155), respectively. As of patients who visited in 2008, the proportion of cirrhotic patients associated with alcohol was 22.9%, which increased to 43.9% in 2015. The proportion of patients with hepatitis B was 54.2% in 2008, and declined to 27.2% in 2015. The proportion of hepatitis C patients was 12.5% in 2008 and 13.3% in 2015. The most common complication of enrolled patients was ascites (19.1%, N = 256), which was followed by variceal bleeding (14.4%, N = 193). The percentage of Child-Pugh class C in alcoholic liver cirrhosis patients was 4.5% in 2008, which came to 33.5% in 2015. In accordance with this, the average MELD score (11.4 -> 13.7) and complication rates were on increasing trend (36.4%-> 65.8%). Whereas, with regard to patients suffering from hepatitis B and C, the occurrence rates of complications were rising (12.5%->38.6%) but the percentage of Child-Pugh class C (0.0% -> 2.1%, 0.0% -> 0.0%, respectively) and MELD score (9.9 -> 10, 9.1 -> 10.7, respectively) were not on meaningful increment, neither on the decrease. Regarding to causes of death, variceal bleeding was the most common cause of death (43.2%) and the second cause was hepatic failure (27.0%).







Conclusions: The progression status and complication rates in patients with alcoholic liver cirrhosis are on worsening tendency. On the other hand, as for patients with viral hepatitis, there was no significant difference in the occurrence rates and disease progression status between in 2008 and 2015. A better understanding of these trends in liver cirrhosis related morbidity and mortality can be instrumental in steering future healthcare policies.

Keywords: Liver cirrhosis, Variceal bleeding, Hepatic failure

PE-113

Laparoscopic Management of Cholelithiasis in Patients with Chronic Liver Disease: A 10-Year Experience

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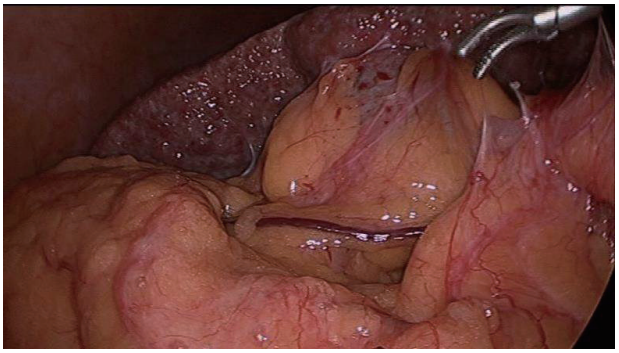
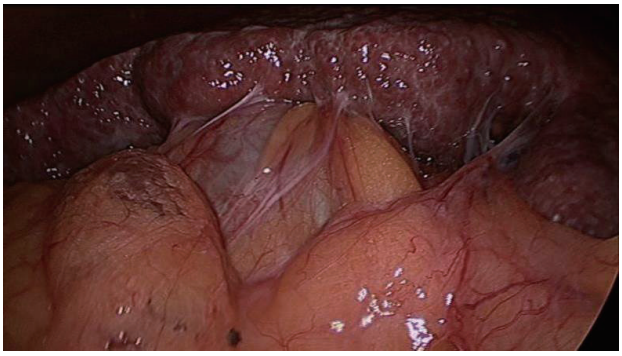
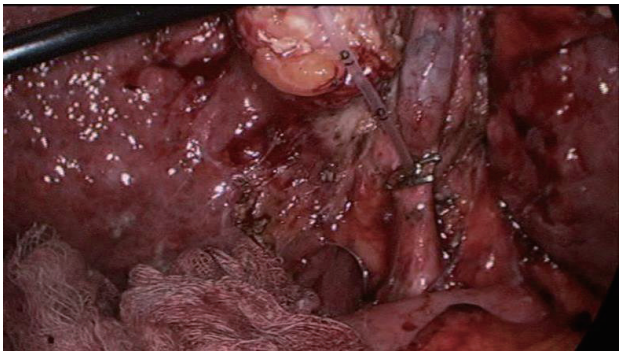
Aims: Laparoscopic cholecystectomy (LC) is usually contra-indicated in patients with chronic liver disease (CLD) due to associated morbidity and mortality. Here we present our 10-year experience of performing laparoscopic cholecystectomy in patients of CLD.

Methods: Analysis of patients of CLD who underwent LC during the period from January 2007 to December 2016 was done. Pre-operative Child Turcot Pugh grade(CTP) and MELD scores, intraoperative parameters as well as perioperative morbidity, mortality and hospital stay were recorded.







Results: Laparoscopic cholecystectomy (LC) was performed in 113 patients with CLD. CTP grade A was seen in 86 patients while 22 patients were grade B and grade C was in 5 patients.

Mean MELD score was 9.5 ± 5.2. Choledocholithiasis was seen in 5 patients (4.4%) for which prior endoscopic clearance was done. 8 patients (7%) required subtotal cholecystectomy. We performed intra-operative cholangiography in 11 patients (9.7%) Mean operating time was 2.1 ± 1.1 hours. Mean intra-operative blood loss was 45 ± 20 ml. Only 2 patients (1.7%) required conversion due to extensive adhesions and collaterals. Perioperative blood transfusion was not required. 4 patients (3.5%) had major morbidity (Clavien Dindo > 3) in the form of bile leak and 1 patient had transient decompensation. Out of these, 3 had CTP grade C (75%). There was no mortality. Median hospital stay was 2 days.

Conclusions: Laparoscopic cholecystectomy is safe approach for management of cholelithiasis in patients with CLD. A meticulous and patient approach and pre-operative optimization is imperative for favorable outcomes.

Keywords: Chronic liver disease, Cholelithiasis, Laparoscopic cholecystectomy

PE-114

Helicobacter Pylori Infection in Cirrhotic Patients with Portal Hypertensive Gastropathy

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Aims: *Helicobacter pylori* infection is a major etiological factor of peptic ulcer disease (PUD). It is also supposed to be a risk factor for the most frequently encountered PUD in patients with liver cirrhosis. It is suggested to be a synergistic effect of *H. pylori* on liver cirrhosis with portal hypertensive gastropathy (PHG).The aim is to study *H. pylori* infection in cirrhotic patients with PHG, determine the proportion of *H. pylori* in cirrhotic patients with PHG and association between *H. pylori* infection and severity of portal hypertensive gastropathy (PHG).

Methods: A hospital based analytic study was carried out on 80 PHG patients diagnosed by OGD during 2017. *H. pylori* infection was detected by rapid urease test and then it was also compared with PHG severity according to Baveno Classification (2002).

Results: *H. pylori* positivity was noted in 39% (n = 31) of PHG patients and 61% (n = 49) of PHG patients were *H. pylori* negative. In mild PHG patients, *H. pylori* was positive in 33% (n = 13 of 40) whereas, in severe PHG patients, it was positive in 45% (n = 18 of 40). The prevalence was higher in severe PHG patients. But, the relationship between *H. pylori* infection and PHG was not significant (*P* value – 0.25).

Conclusions: Among 80 COL patients with PHG, *H.pylori* positivity was 39%. Although there was no statistically significant between *H. pylori* infection and cirrhotic patients with PHG, the prevalence of *H. pylori* was higher in severe PHG patients.

Keywords: H Pylori infection, Portal hypertensive gastropathy, Cirrhosis, Severity of portal hypertensive gastropathy

Liver Failure,Acute

PE-115

Biofabricated Silver Nanoparticles of Aqueous Extract of Bassia Longifolia L Leaves Mitigates Diethylnitrosamine Induced Hepatocellular Carcinoma in Wistar Rats: A Novel Approach for Liver Therapy

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Aims: Hepatic cancer is one of the deadly diseases in which liver cell multiplication occurs and the major cause of mortality associated with cancer. NF-kB plays its role by regulating the activation via inflammatory responses, cell survival and proliferation. Natural based products subsequently plays an important role in supressing proinflammatory mediators via nuclear factor –Kappa beta (NF-kB) pathway. *Bassia longifolia* L leaves used in liver cancer therapy. The latest study was therefore designed to investigate the beneficial effects of phytofabricated silver nanoparticles (BLAgNPs) using the extract of Bassia longifolia leaves as NF-kB hepatic cancer inhibitors.

Methods: Phytofabricated silver nanoparticles using *Bassia longifolia* L aqueous extract (BLAgNPs) which acts as reducing and capping agent. Biofabricated silver nanoparticles (BLAgNPs) were characterized by UV spectroscopy, FTIR, X-ray diffraction, and Field Emission Scanning Electron Microscope. A cancer causing agent diethylnitrosamine and phenobarbitone as a promoter used to induce the Hepatic cancer in rats and rats were treated with different doses of BLAgNPs for 16 weeks. The anticancer effects was evaluated via *in vitro* cytotoxic activity on HUH (hepatic cancer) cell line and by determining biochemical parameter in the wistar rats.

Results: Results suggested that BLAgNPs revealed peak at 418 nm in UV spectrophotometer with spherical structure as shown in FESEM image and gives crystalline peak of silver in XRD diffraction. Different doses of BLAgNPs significantly reduced the serum marker enzymes, raised the levels of enzymatic and non-enzymatic antioxidant profile, and lessen the levels of inflammatory markers (IL-6, TNF-alpha and IL-10) via NF-kB pathway in rats in dose dependent manner.

Conclusions: Biofabricated silver nanoparticles revealed remarkable productive effects on hepatic cancer in rats and by regulating cytokines and NF - kB its serve as a novel targeted therapy for hepatic cancer.

Keywords: Bassia longifolia L, Silver nanoparticles, Diethylnitrosamine, Cytokines

PE-116

Downregulation of PGC-1 Leads to Decreased Expression of Mitochondrial Antioxidant Enzymes in the Mouse Model of Obstructive Cholestasis

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Aims: Several studies have indicated that cholestatic liver damage is mitochondria-mediated. However, the precise mechanism by which hydrophobic bile salts cause mitochondrial dysfunction is not clear. In this study, we intended to determine the pathogenesis of cholestatic liver injury associated with peroxisome proliferator activated receptor co-activator 1α (PGC-1α).

Methods: The mouse model of cholestatic livers was generated by surgical ligation of the bile duct (BDL), and the mouse model of fibrosis was developed following serial administration of thioacetamide. Next, after obtaining liver specimens on scheduled days, we compared the expression of the antioxidant enzymes (superoxide dismutase2 [SOD], catalase, and glutathione peroxidase-1[GPx]), and PGC-1α in livers from mice with fibrosis and cholestasis using western blotting, immunohistochemistry and immunofluorescence.

Results: We found that a cholestatic liver exhibits lower expression of antioxidant enzymes, such as SOD, catalase, and PGC-1α. Contrastingly, a fibrotic liver exhibits higher expression of antioxidant enzymes and PGC-1α. In addition, cholestatic livers were found to show significantly lower expression of pro-apoptotic markers (Bax) than that seen in fibrotic livers.

Conclusions: It was well known that overexpression of PGC-1α increases mitochondrial antioxidant enzyme expression, and vice versa. Thus, we concluded that obstructive cholestasis decreases expression of PGC-1α, which leads to decreased expression of mitochondrial antioxidant enzymes, rendering mice with cholestatic livers vulnerable to ROS-induced cell death.

PE-117

The Role of P-JNK Expression on Hepatocyte Necrosis and Autophagy in the Cholestatic Liver

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Aims: Clinically, liver fibrosis and cholestasis are two major disease entities, ultimately leading to hepatic failure. Although autophagy plays a substantial role in the pathogenesis of these diseases, its precise mechanism has not been determined yet.

Methods: Mouse models of liver fibrosis or cholestasis were obtained following the serial administration of thioacetamide or surgical bile duct ligation (BDL), respectively. Next, after obtaining liver specimens at specific time points, we compared the expression of apoptotic (cleaved caspases), necrotic (phospho-c-Jun N-terminal kinase [p-JNK] and CD68), and autophagy markers (microtubule-associated protein light chain 3B [LC3B] and p62) in the fibrotic or cholestatic mouse livers, using polymerase chain reaction, western blot analysis, immunohistochemistry, and immunofluorescence.

Results: Following BDL, although there was a time-dependent increase of necrotic markers (p-JNK and CD68), no significant expression changes were detected in pro-apoptotic markers (cleaved cascades) over time. In addition, autophagy marker studies indicated that whereas autophagy was upregulated in fibrotic livers, it was downregulated in cholestatic livers. We also observed mild to moderate activation of p-JNK in fibrotic livers, whereas cholestatic livers demonstrated a significantly higher p-JNK activation.

Conclusions: Whereas fibrotic livers exhibited a mild to moderate increase in p-JNK expression related with the induction of autophagy and apoptotic cell death, cholestatic livers exhibited a marked increase in p-JNK expression which could be associated with the reduction of autophagy and a subsequent increase in necrosis.

PE-118

Antioxidant Action of Hypoxic Conditioned Media from Adipose-Derived Stem Cells in the Hepatic Injury of Expressing Higher Reactive Oxygen Species

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Aims: Almost all liver diseases are known to be accompanied by increased levels of ROS, regardless of the cause of the liver disorder. However, little is known about the role of hypoxic-conditioned media (HCM) in the view of pro-oxidative/antioxidative balance.

Methods: Normoxic-conditioned media (NCM) and HCM were obtained after culturing ASCs in 20% O2 or 1%O2 for 24 hours, respectively. Their effects on the expression of various markers reflecting pro-oxidative/antioxidative balance were investigated in both *in vitro* (thioacetamide-treated AML12 cells) and *in vivo* (partially hepatectomized mice) models of liver injury, respectively.

Results: HCM treatment induced the higher expression of antioxidant enzymes, such as SOD, GPx, and catalase than did NCM in the *in vitro* model of liver injury. We also found that HCM increased the expression of NRF2. The *in vivo* models of liver injury consistently validated the phenomenon of upregulated expression of antioxidant enzymes by HCM.

Conclusions: We thus could conclude that HCM provides protection against ROS-related toxicity by increasing the expression of antioxidant enzymes, in part by releasing NRF2 in the injured liver.

PE-119

Effect of Extracorporeal Bioartificial Liver Support System on Fulminant Hepatic Failure Rabbits

Nursultan Kydyr, Samat Issakov

General surgery, National Research Center for Maternal and Child Health, Kazakhstan

Aims: To evaluate the possibility of using cultured human hepatocytes as a bridge between bioartificial liver and liver transplantation.
Methods: In this experiment, the efficacy of extracorporeal bio artificial liver support system (EBLSS) consisting of spheriodal human liver cells and cultured hepatocytes supernatant was assessed *in vivo* using galactosamine induced rabbit model of fulminant hepatic failure.
Results: There was no difference of survival between the two groups of rabbits, but in the supported rabbits serum alanine aminotransferase, total bilirubin and creatinine were significantly lower and hepatocyte necrosis was markedly milder than those in control animals. In addition, a good viability of human liver cells was noted after the experiment.
Conclusions: EBLSS plays a biologic role in maintaining and compensating the function of the liver.
Keywords: Bioartificial liver support system, Fulminant hepatic failure, Hepatocytes, Liver transplantation

PE-120

Immunocorrecting Action of Roncoleukin in Patients with Acute Cholangitis in Various Ways of Application

Talgat Beisenbayev, Rysmakhanov M.S., Mussin N.M.

Aktobe Medical Center, Kazakhstan

Aims: No doubt, the involvement of the immune system in the development of purulent cholangitis. Developing against the background of dysfunction of the immune system, secondary immune deficiency and endogenous intoxication with acute cholangitis determines the severity of the course and high lethality. To study the indices of immunological reactivity in patients with acute cholangitis in use of Roncoleukin in erythrocyte membranes.
Methods: The study included 64 patients with acute purulent cholangitis who was on inpatient treatment in the surgical department of "Aktobe Medical Center", Aktobe from 2016 to 2018. The content of immunoglobulin classes A, M, G of complement was determined on a biochemical analyzer "Cobos integro". The CEC content was determined by precipitation with a 3.5% polyethylene glycol solution on a spectrophotometer at a wavelength of 450 nm. CD3 +, CD4 +, CD8 +, CD20 +, CD25 +, CD56 +, CD95 + - were determined using monoclonal antibodies. IL-2 in blood plasma was examined with the ProCon kit using the solid-phase enzyme-linked immunosorbent assay.
Results: The analysis showed shifts characteristic for secondary induced immune dysfunction. There was a significant tendency to normalization of the immunophagocytic link, which was confirmed by the normal content of CD20 +, CD25 +, CD56 +, CD95 +, HLA - cells and immunoregulatory index.
Conclusions: Thus, according to some indicators of immunograms, there is an accelerated dynamics of regression of signs of secondary immune deficiency when included in the complex of conservative therapy of Roncoleukin in autologous erythrocyte membranes in patients with acute cholangitis.
Keywords: Roncoleukin, Acute cholangitis, Cytokine

PE-121

Acute Liver Failure in Kazakhstan

Zhanna Kozybayeva, Yermakhan Assylkhanuly

University Medical Center, Kazakhstan

Aims: Acute liver failure (ALF) is a life-threatening condition that can rapidly progress into coma and death due to the cerebral edema and multi-organ dysfunction. The ALF etiology and risk factors have been investigated in West Europe, North America, and Asia; however, there are still no published data about the causes and prognosis of ALF in Central and East European countries. The aim of our study was to analyze the causes, outcomes, and prognostic factors of ALF in patients referred to tertiary care center in Kazakhstan.
Methods: A total of 12 consecutive patients admitted to the tertiary care center (one of two university-level medical centers in Lithuania) over the period of January 2012 and December 2017 and who fulfilled the entry criteria of ALF (presence of hepatic encephalopathy (HE) and prothrombin international normalized ratio (INR) >1.5) were included into a prospective study.
Results: In our study the most frequent causes of ALF were acute viral hepatitis B (21.4%), drug-induced hepatitis (21.4%), and indeterminate hepatitis (17.9%); other etiologies included Budd-Chiari syndrome (10.7%), ischemic hepatitis (10.7%), Wilson's disease (7.1%), Amanita phalloides-induced liver damage (3.6%), acute fatty liver of pregnancy (3.6%), and malignant infiltration of the liver (3.6%). Among patients with drug-induced liver injury, only one case of acetaminophen poisoning was diagnosed. Clinical status of 9 persons in all patients with ALF corresponded to criteria for liver transplantation (LT) (one liver transplantation was performed), 6 of them had contraindications, and 13 patients did not fulfill requirements for urgent LT. The patients' survival rate in these groups was 11.1%, 16.7% and 69.2%, respectively. In 27 non-transplanted patients univariate analysis revealed the grade of HE on the day of enrolment, total serum bilirubin, pH, and prothrombin INR as risk factors for death from ALF. Multivariate logistic regressive analysis determined only prothrombin INR >3.24 and serum pH <OR = 7.29 as independent predictors of lethal outcome in ALF.
Conclusions: Acute viral hepatitis B, drug-induced liver injury, and indeterminate hepatitis are the main ALF causes in Kazakh-

stan. In non-transplanted patients, the main predictors of lethal outcome were severe coagulopathy and metabolic acidosis. Improvement of liver donation system for urgent liver transplantation is essential requirement for amelioration of ALF patient's survival.

Keywords: Acute, Liver, Failure, Hepatitits

PE-122

Acute Liver Rejection Values of Doppler US Measurements

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University Medical Center, Kazakhstan

Aims: To prospectively evaluate accuracy and predictive values of Doppler ultrasonographic (US) measurement of portal blood velocity (PBV) and splenic pulsatility index (SPI) in diagnosis of clinically relevant acute rejection in patients with clinicobiochemical hepatic dysfunction after orthotopic liver transplantation (OLT).

Methods: Study was approved by the institutional review board, and protocol conformed to ethical guidelines of Declaration of Helsinki. Patient informed consent was obtained. In 17 patients with OLT (13 men, four women; mean age, 48 years; range, 27-64 years), PBV and SPI were measured at Doppler US within 48 hours before or after liver biopsy for clinically suspected acute rejection. Biopsy specimens were assigned scores according to Banff method, and rejection activity index (RAI) was calculated. RAI score of 4 or greater was considered clinically relevant acute rejection. Doppler US parameters were analyzed as absolute values and as percentage point changes with respect to values obtained at last examination before rejection was suspected. Information from two Doppler US parameters was combined; Doppler US composite index was calculated. Statistical tests were conducted to assess accuracy, sensitivity, specificity, and predictive values of Doppler US parameters in diagnosis of graft rejection.

Results: Clinically relevant acute rejection was diagnosed in nine patients. Median time from OLT until histologic diagnosis of acute rejection was 8 days (range, 5-20 days). Rejection was associated with a marked reduction in mean PBV (-43% +/- 5 [standard error of the mean]) and a slight increase in SPI (+12% +/- 16). The calculated Doppler US composite index was strictly related to severity of rejection ($P < .001$). When applied retrospectively, this index had good accuracy (88%) for prediction of rejection (specificity, 89%; sensitivity, 86%; negative predictive value, 94%).

Conclusions: During the first weeks after OLT, a marked decrease in PBV associated with increased SPI supports suspicion of clinically relevant acute rejection.

Keywords: Acute, Liver, Rejection, Doppler

PE-123

Organs Failure Prevention for Patients with Hepatorenal Syndrome

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Aims: Hepatorenal Syndrome (HRS) plays an important role in patients with liver cirrhosis. To determine the dynamics of the severity of the condition and prediction of the estimated risk of mortality (ERM) patients with HRS using MARS-therapy and Plasmapheresis.

Methods: The study included a group of 9 patients with HRS in ages from 18 to 66 years. 6 patients of the main group received MARS-therapy and Plasmapheresis. Inside the main group investigated patients were divided into 3 groups (moderate, severe and very severe) depending on the number of points. Assessment of the dynamics of flow multiple organ failure (MOF) performed before treatment and 3-5 days of treatment.

Results: According to the results of the intragroup analysis revealed statistically significant dynamic changes in the main group for the subgroup of moderate severity. The decrease in the average scores in the subgroup indicates positive patient outcomes. Comparison between subgroups and the control group showed no statistical differences in the dynamics of APACHE III. The exception was two subgroups moderate groups where there was a statistically significant difference in the initial state - prior to treatment. This is due to the small sample of patients, where the average score was higher APACHE III in the study group than in the control. At subsequent stages of observation for 3-5 day these differences offset due to the patients. The dynamics of the estimated risk of death in 1st and a 2nd subgroup of the main group shows a statistically significant decreased this indicator.

Conclusions: The use of MARS-therapy and Plasmapheresis treatment may be considered appropriate in someone the complex therapy of patients to preventing the MOF. The appropriate use of MARS-therapy and Plasmapheresis in patients with HRS remains controversial and requires further evidence by the researches.

Keywords: Liver failure, Organs failure, Detoxicy

PE-124

The Characteristics of Acute-on-Chronic Liver Failure Patients Based on Two Different Definitions: Prospective Korean Acute-on-Chronic Liver Failure Study

Do Seon Song[1], Hee Yeon Kim[1], Young Joo Jin[2], Dong Hyun Sinn[3], Eileen L. Yoon[4], Chang Wook Kim[2], Young Kul Jung[5], Ki Tae Suk[6], Sang Soo Lee[7], Hyun Chin Cho[7], Chang Hyeong Lee[8], Hwi Young Kim[9], Tae Hun Kim[9], Baek Gyu Jun[10], Hyung Joon Yim[5], Sung Eun Kim[11], Sung Won Lee[1], Jung Hyun Kwon[1], Seong Hee Kang[12], Soon Koo Baik[12], Byung Seok Lee[13], Jae Young Jang[14],

Jeong Ill Suh[15], Hyoung Su Kim[16], Seong Woo Nam[17], Hyeok Choon Kwon[17], Young Seok Kim[18], Sang Gyune Kim[18], Hee Bok Chae[19], Jin Mo Yang[2], Joo Hyun Sohn[20], Jung Gil Park[21], Heon Ju Lee[21,] Yoon Jun Kim[22], In Hee Kim[23], Ju Yeon Cho[24], Man Woo Kim[24],Sang young Han[25], Won Kim[26], Dong Joon Kim[6], on behalf of the Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

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Aims: We aimed to investigate the prevalence and short-term mortality of acute-on-chronic liver failure (ACLF) patients according to Asian Pacific Association for the Study of the Liver ACLF Research Consortium (AARC) and European Association for the Study of the Liver Chronic Liver Failure Consortium (EASL-CLIF) definition.

Methods: We collected prospective data for acutely deteriorated patients with chronic liver disease in Korea.

Results: A total of 982 patients were enrolled. The mean age was 54.7 years, and 76.5% was male. Most patients (92.3%) had cirrhosis, and the most common cause of chronic liver disease was alcohol. The prevalence of ACLF based on the AARC and EASL-CLIF definitions was 14.2% and 20.5%, respectively. In AARC ACLF patients, ascites and jaundice as acute deterioration and alcohol, toxic material, and hepatotropic virus as precipitating factors were more frequent than EASL-CLIF ACLF patients. On the other hand, variceal bleeding and bacterial infection as acute deterioration and precipitating factors were more frequent in EASL-CLIF ACLF patients. The 28-day and 90-day mortality of ACLF patients were 23.0% and 39.0% based on AARC definition, and 26.4% and 43.9% based on EASL-CLIF ACLF definition. Patients who met both ACLF definitions showed significantly lower 28-day survival rate than those who met only one ACLF definition ($P < 0.05$), and significantly lower 90-day survival rate than those who only AARC ACLF definition ($P = 0.001$), but not EASL-CLIF ACLF definition ($P = 0.055$). These short-term mortality rates were significantly higher than those without ACLF (all $P < 0.001$). In patients with ACLF, cirrhosis was not significant factor for short-term mortality. In addition, previous decompensation was also not significant factor, even within a year.

Conclusions: The AARC ACLF patients and EASL-CLIF ACLF patients had different characteristics. However, the patients with ACLF based on both AARC and EASL-CLIF definitions showed significantly higher mortality rate than those without ACLF.

Keywords: Acute-on-chronic liver failure, Mortality, Prevalence

PE-125

Production of Steroid Drug Precursor Used in Treatment of Chronic Liver Diseases

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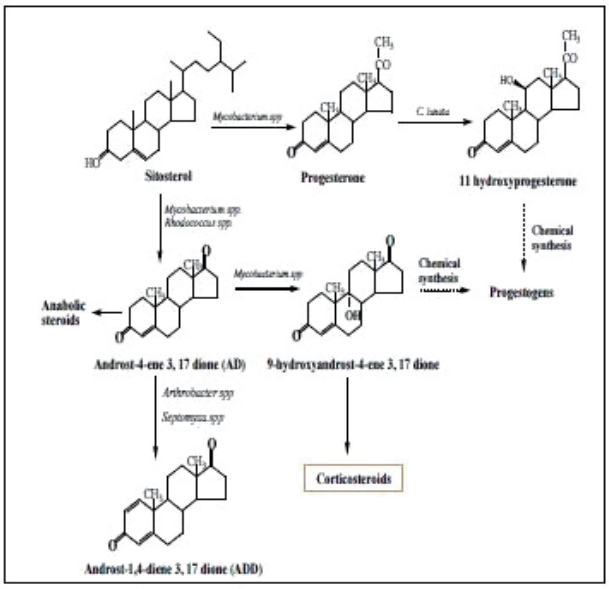
Aims: Use of steroidal drugs in liver dysfunction is reported by different research groups. Corticosteroids are one of them. Reduced inflammation is reported in acute liver failure by glucocorticosteroid. These drugs blocks receptor proteins in cytoplasm and alter protein synthesis. The complex of steroid drug and receptor interacts with DNA and blocks production of inflammatory biochemical. The production of these important steriodal drugs is done by complex chemical process. Androst-4-ene 3, 17 dione (AD) and 9-hydroxyandrost-4-ene 3, 17 dione (9-OH-AD) are current precursors of corticosteroids. The present study was aimed at production of androstenedione by using microorganism and screening of efficient substrate carrier solvent.

Methods: Two strains of *Mycobacterium species* were used for two different bioconversion reactions. For phytosterols to AD conversion *Mycobacterium fortuitum* subsp. *fortuitum* NCIM 5239 was used. Optimized medium B was used as incubation medium. For hydroxylation of AD to 9-OH-AD, *Mycobacterium* sp. NRRL B-8119 was used. Analysis of products was done by

quantitative thin layer chromatography.

Results: As compared with control, ethanol and DMF exhibits enhanced biotransformation of AD after 144 h incubation time. But in case of hydroxylation, organic solvents are suppressed the production of 9-OH-AD. Vegetable oils in both bioconversion reactions showed nearly 90-95 mol% conversion of products. Sunflower oils exhibited nearly 88 and 92 mol% conversion of AD and 9-OH-AD respectively.



Bioconversion of steroid substrate into different intermediate drugs.

Conclusions: Production of AD and 9-OH-AD could be optimized for industrial production of corticosteroids. Organic solvents and oils may be used as substrate carriers to enhance industrial scale production of live failure drugs.

Keywords: Acute liver failure, Corticosteroids, Steroid drugs, Mycobacterium

Liver, Infectious Disease

PE-126

Pattern of Liver Disease at Tertiary Level Care in Nepal: Hospital Based Retrospective Study

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Aims: - To study distribution and pattern of liver disease in a tertiary care center provides an overview of disease pattern in a community. -To plan and prioritizing strategies to treat the diseases and reduce their burden in the community.

Methods: A retrospective study was conducted among patients admitted to the Liver unit, Sarvanga Hospital Lalitpur from April 13, 2018 to October 16, 2018. Demographic profile and disease pattern was studied. Descriptive analysis was used to calculate frequencies and percentage and and their relations.

Results: Male to female ratio was 2.3:1. The mean age was 41.9 (SD 14.8). Median hospital stay was 8.0 days (Q25-75 6.0-12.0). The top three diseases were alcoholic liver disease 50 (38.5%), viral hepatitis 44 (33.8%), and liver abscess 11 (8.5%). Fifty (38.5%) patients had acute, 74 (56.9%) had chronic liver disease and 6 (4.6%) were malignancy. The main cause of acute disease were infections 41 (82.0%) especially Hepatitis E Virus (HEV). HEV was associated with acute liver failure and pregnancy which was 4 (18.2%) and 2 (12.5%) respectively. Chronic diseases were caused by alcohol 45 (60.8%) followed by infection of hepatitis B and C viruses 11 (14.8%). Cirrhosis was diagnosed in 37 (28.5%) with alcohol as the main cause.

Conclusions: Majority had chronic liver disease (CLD), mostly due to alcohol, HBV and HCV. Alcohol was the leading cause of cirrhosis. Prevalence of Hepatitis E was found to be high in acute illness. Therefore, an initiative needs to be taken to decrease alcohol consumption along with HEV, HBV and HCV transmission through community health program.

Keywords: Alcohol, Cirrhosis of liver, Hepatitis, Liver diseases

PE-127

Possibilities of Application of Endoscopic Techniques in the Diagnosis and Treatment of Echinococcosis of the Liver

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Aims: To improve the quality of diagnostics and treatment of the liver echinococcosis by using endoscopic technologies.

Methods: The results of laparoscopic endocystectomy in 78 patients treated for liver echinococcosis compared to cystectomy by laparotomy in 124 patients are presented.

Results: Optimal characteristics for laparoscopic endocystectomy were types CL, CE1-CE3 of cystic echinococcosis according to cystic echinococcosis ultrasonic classification by H.A. Gharbi (1981) modified by World Health Organization (2003) with cysts localized in 2–6 liver segments; partial superficial location of cysts; cyst size not less than 5 cm; no cysts in 1, 7 and 8 liver segments or deeply located cysts of any size, as well as cysts of CE4-CE5 types. Of the 78 cases in which laparoscopic endocystectomy was completed successfully, in 4 patients the surgery was continued by a laparotomy access. The reasons for the continuation with laparotomy were unsuccessful attempts for stable hemostasis at resection of liver fibrous capsule excesses (1 case), presence of large fistula between the cyst and components of the biliary system at the bottom of the fibrous cavity (2 patients), and location of the second cyst in the segment unavailable for laparoscopic manipulation (1 case). The frequency of early complications after laparoscopic endocystectomy was

14.9%. Relapse occurred in 1 (1.1%) patient. Comparative assessment of echinococcosis recurrence risk in different periods (Kaplan–Meier analysis) after laparoscopic interventions and laparotomy, both followed by albendazole treatment, did not identify any statistically significant differences.

Conclusions: Endoscopic technology application in the form of video laparoscopy, diagnostics and treatment endovideoscopy of the residual cavity in the intra- and postoperative periods allows improving the diagnostics quality and treatment results of patients with the liver echinococcosis.

Keywords: Liver, Echinococcosis, Laparoscopic, Treatment

PE-128

Atypical Liver Resections in Liver Alveococcosis

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Aims: To evaluate results of surgical treatment of liver alveococcosis in which atypical resection was performed.

Methods: We analyzed the results of treatment of 15 patients with alveococcosis of the liver for the period from 2011 to 2017, who had atypical resection of the liver in various volumes.

Results: There were 10 men (55, 5%) and 8 women (44, 5%). The age of patients was ranged from 9 to 63 years old. Four patients had a parasite lesion of the right and left lobes of the liver, which produced atypical resections of both lobes. One of them had lesion of both lobes combined with the germination of the duodenal ulcer into the serosa. This patient got an atypical resection of the liver and removal of the parasite with a wedge resection of the duodenum, followed by closure of the resulting defect. The second patient had three lesions, two marginal removed with atypical resection. Alveococcal node, localized in the central segments (first, fourth and eighth), grew into the inferior vena cava, which was not resectable. In percentage terms, the lesion was localized in both lobes in 6 (33,3%), in the right lobe in 9 (50%), in the left lobe in 3 (16,3%) of patients. The duration of the disease ranged from 1 month to 3 years. Six patients got resection of two segments of the liver, and the rest patients were resected in one segment of the liver. Blood loss varied from 150 to 800 ml, and the duration of the operation ranged from 1 hour to 6 hours. There were no postoperative complications (hepatic failure, bile-elimination) in patients with abnormal liver resection. Lethal outcomes also were not observed in this group.

Conclusions: Atypical resection is a radical treatment for liver alveococcosis. In case of regional localization, small alveolar nodes or multiple and bilobar liver damage, we consider it expedient to perform an atypical resection of the liver.

Keywords: Atypical liver resections, Liver alveococcosis, Small liver resection

PE-129

Surgical Aspects Treatment of Liver Echinococcosis

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Aims: One of the urgent problems at the present stage is the surgical treatment of liver ehinococcosis.

Methods: In the surgery department of the Kyzylorda Regional Medical Center between 2013-2018 various 108 operations to the patient in connection with echinococcosis liver. 73 patients (67,5%) were women, 35 (32,4%) were men aged 16 to 58. Location in the right lobe of the liver–64 (59.2%), in the left side–34 (31,4%), in both lobes of the liver–10 (9.2%). Hydatid cyst of the liver, recurrent 8 (7,4%). The situation is complicated by fistulas, cystobiliary 17 (15,7%) of the patient. It was manufactured by the following operations: laparoscopic echinococcectomy - 22(20,3%), bisegmentectomy-1 (0,9%), pericystectomy–8 (7,4%), echinococcectomy–77 (71.2%), including: marsupialisation–1 (0,9%), omentopexy–7 (6,4%), abdominal cysts–13 (12%), capitonnage of the residual cavity–56 (51.8%).

Results: In the postoperative period, 22 (20.3%) patients had complications. Of these, 13 (59%) in the form of exudative pleurisy, ended with a puncture of the pleural cavity. Suppuration of the residual cavity 7 (31,8%) patients, 2 (9%) patients, had relaparotomy drainage of abscess, 1 (4,5%) patients underwent laparoscopy, drainage of abscess, 4 patients (18,1%) performed puncture of the residual cavity under ultrasound control drainage and Pigtail type. Complications of the biliary tract in 2 (9%), a Pigtail catheter under ultrasound control. On 8 - 16 weeks after surgery, the bile fistula is closed, the catheter is removed. Hyperthermia in the postoperative period was in 20 (18.5%) patients, they were carried out antibacterial therapy and infusion therapy additionally prescribed fractional plasmapheresis. Postoperative hyperthermia occurred in patients who underwent omentopexy and cyst abomination. There was no mortality.

Conclusions: To prevent complications such as abscess of the residual cavity and hyperthermia, it is necessary to choose a radical operation. If it is impossible to perform a radical operation, then it is necessary to carry out capitonage of the residual cavity with adequate drainage.

Keywords: Liver, Echinococcosis, Surgical, Treatment

PE-130

A Case of Acute Hepatitis E Mimicking Autoimmune Hepatitis

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Aims: Hepatitis E Virus (HEV), an enterically transmitted virus, occurs mainly in developing countries and endemic areas. However, sporadic cases of acute hepatitis E have been reported in developed countries. Swine seem to function as a reservoir for HEV. We experienced a case of acute hepatitis E in 41-year-old man. The patient did not have any travel history to an HEV-endemic area.
Methods: Here we report a case of acute hepatitis E mimicking autoimmune hepatitis.
Results: A 41-year-old man visited hepatology department for jaundice. He was diagnosed with autoimmune hepatitis 2 weeks ago in other hospital. He had been taking prednisolone for 2 weeks for autoimmune hepatitis. He had no medical past history. There was no history of alcohol or herbal medication. He was not performed a liver biopsy. Blood tests performed at other hospitals showed serum bilirubin levels of 10.3 mg/dL. Serum ANA was positive and serum titer was 1: 160. Abdominal CT scan perfomed showed periportal edema, consistent to acute hepatitis. Laboratory findings showed altered liver enzymes with serum aspartate aminotransferase (AST) 89 IU/L, alanine aminotransferase (ALT) 270 IU/L, alkaline phosphatase 101 IU/L, total bilirubin 2.5 mg/dL, IgG 1529 mg/dL. Prothrombin time (INR) was 1.1. The serological tests revealed positive ANA (titer 1:80), ASMA positive with negative tests for anti-LKM1, anti-dsDNA, anti-mitochondrial antibody. Viral serology was negative for HBsAg, anti-HBs, IgM anti-HBc, IgM anti-HAV, anti-HCV with undetectable RNA of HCV. HEV IgM was positive with HEV IgG was negative. Liver biopsy revealed atypical findings for autoimmune hepatitis. Immunosuppressive therapy was stopped. He recovered after conservative treatment without complication.
Conclusions: Hepatitis E should be considered in the differential diagnosis in all cases of unexplained acute hepatitis in developed countries, regardless of travel history. Careful history taking and serologic test is required.
Keywords: Acute hepatitis E, Autoimmune hepatitis, Sporadic, Serologic test

PE-131

HIV-HCV Coinfection: Prevalence and Associated Risk Factors in the Western Region of Nepal

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Aims: Both Human Immunodeficiency virus (HIV) and Hepatitis C virus (HCV) are blood borne viruses transmitted primarily through sexual contact and injection-drug use. Because of these similar modes of transmission, adults at risk for HIV infection are also at risk for HCV infection. The rates of HIV-HCV coinfection varies with geographical regions, risk factors, and modes of transmission. This study aimed to explore the prevalence of HIV-HCV coinfection and associated risk factors for HCV in HIV infected individuals in Western Nepal.
Methods: This cross-sectional study enrolled 192 HIV positive individuals visiting Antiretroviral Therapy Centre of Western Regional Hospital (WRH), Pokhara, Kaski between June and December, 2017. Consent was taken prior to collection of blood samples. The socio-demographic information and associated risk factors for the viral infection were recorded following a standard format. Blood samples were processed to determine serum anti-HCV antibodies by enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence immunoassay (ECLIA).Data were statically analysed using SPSS software.
Results: The result suggested 4.17% (8/192) prevalence of HIV-HCV coinfection. Although not statistically significant, the sero-prevalence of HCV was highest for male (6/84, 7.14%) than female (2/108, 1.85%).Additionally, sero-prevalence was highest in age group 30-39 years 5(2.6%) followed by 40-50 years 2(1.04%).Intravenous drug use was found to be significantly associated with HIV-HCV coinfection ($P < 0.05$).
Conclusions: Despite effective anti-retroviral therapy, hepatitis and liver-diseases represents major cause of deaths among HIV-HCV coinfected patients suggesting a mandatory screening for HCV in HIV infected individuals. As intravenous drug use is associated risk factor, addressing the risk environment for intravenous drug users could minimize the cases of HIV-HCV coinfection in our community.
Keywords: HIV, HCV, Coinfection, Western Nepal

PE-132

Seroprevalence of Hepatitis C Virus and Tuberculosis Co-Infection among HIV Infected Individuals

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Aims: HIV is the chronic viral infection documented worldwide. It infects and destroys helper T cells (CD4) leading to number of immunological deficiencies among which Hepatitis-C Virus (HCV) and Tuberculosis (TB) are major. HCV is a RNA virus that infects the liver and is a leading cause of deaths in HIV/HCV co-infected patients. Tuberculosis is a disease caused by *Mycobacterium tuberculosis* which affects mainly the lungs and is transmitted exogenously. The aim of this study was to examine HCV and tuberculosis co-infection in HIV positive patients to recognize the prevalence rates of co-infection in these patients.
Methods: A hospital based cross-sectional study was carried out on 90 HIV positive individuals visiting ART center of Western

Regional Hospital. The patients were counseled and samples were taken. Samples were processed by ELISA and analyzed by SPSS. HCV, pulmonary TB and extra pulmonary TB were measured for all participants.

Results: For HCV 82(91.9%) were negative and 8(8.1%) were positive and for pulmonary TB, 88(97.8%) were negative and 2(2.2%) were positive whereas for extra pulmonary TB, 9(10%) were positive and 81(90%) were negative. In multivariable analysis, these co-infections were found higher in age group 35-50, male and married. Prevalence of HCV and pulmonary TB showed significant value (p-0.039). Similarly, significant value was also shown in HCV infection among male and IV drug users whereas in TB, significant value was shown among smokers.

Conclusions: The result of our research suggests the need of regular screening of the patients to detect these co infections so that it can aid to reduce mortality of HIV infected individuals due to HCV and TB.

Keywords: Prevalence, Co-infection, HIV, HCV, TB, ELISA

PE-133

Morphology and Histopathological Study of a Liver, Having Inflamed Left and Quadrate Lobe

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Aims: Chronic liver disease is the common cause of death in the developing countries now-a-days. The disease increases liver related morbidity and mortality, and often increases the risk of other comorbidities such as type 2 diabetes and cardiovascular disease.

Methods: During the routine dissection of undergraduate students at the Department of Anatomy, All India institute of Medical Sciences, Jodhpur India, it was observed in a 74 year old male cadaver the liver was completely covered by the greater omentum. Liver was dissected out to study the morphological and histopathological changes.

Results: The weight of the liver was 2.3 kg. The maximum vertical and transverse diameter of the liver was 16.9 cm and 18.2 cm respectively. Diameters of different lobes of liver are mentioned in table no. 1. The right lobe and caudate lobe of the liver were normal. The left lobe and quadrate lobe of the liver were inflamed. The diameters of the left and quadrate lobe of liver were more than the normal parameters. The histopathological study of the liver was also done using H& E staining. Fatty liver changes were observed in the histopathology.

Table 1. Showing the diameter of different lobe of liver

S. No.	Lobe of1	Max. vertical diameter (cm)	Max. transverse diameter (cm)
1.	Right lobe	16.7	8.1
2.	Left lobe	14.5	7.9
3.	Quadrate lobe	9.1	7.6
4.	Caudate lobe	6.0	3.1

Conclusions: There has been an exponential increase in the global incidence and prevalence of liver disease because of the obesity pandemic. In the absence of therapeutic interventions, most of the cases showed increased morbidity and mortality.

Keywords: Histopathology, Morphology, Lobes

PE-134

The Urinary Tract Infection with Liver Cirrhosis Patient

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Aims: To evaluate the incidence of bacterial infections (BI) in liver cirrhosis (LC), the pathogen agents involved, to define the risk factors and impact on prognosis.

Methods: There was a retrospective study that enrolled a total of 25 patients with LC admitted in our clinic between 2018.03-2018.09 (6 months) Clinical, biological and bacteriological data were monitored.

Results: 6 patients (24%) were found with urinary tract infection. 4 patients are female, 2 patients are male. Of the 6 cases with urinary tract infection, the etiologic agent was identified in three: E. coli, Klebsiella, Citrobacter.

Conclusions: In this study, the rate of urinary tract infections in LC is high, because the study was retrospective. We must actively seek infections in all hospitalized patients with LC.

Keywords: Urinary tract infection, Liver cirrhosis

PE-135

Acute Cholestatic Hepatitis Induced by Epstein-Barr Virus Infection in an Adult

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Aims: Acute cholestatic hepatitis without features of infectious mononucleosis is a rare presentation of primary Epstein-Barr virus(EBV) infection, with only several cases previously reported in the medical literature.

Methods: A 24 years old young man with a febrile illness was noted to have a cholestatic picture of deranged liver function tests. Over the following week a progressive obstructive jaundice developed, with no evidence of choledocholithiasis on ultrasound and magnetic resonance cholangiopancreatography. Serological tests for hepatitis A, B, C, E, cytomegalovirus (CMV), leptospirosis were negative. Specific immunoglobulin M antibodies against EBV were detected in his serum and the diagnosis of EBV associated hepatitis was confirmed by polymerase chain reaction testing.

Results: Supportive treatment was implemented and his liver function had normalized 3 months after presentation.

Conclusions: EBV is associated with a wide variety of clinical

manifestations and can present as cholestatic hepatitis with or without features of infectious mononucleosis. While the diagnosis is often suggested by serological testing, EBV polymerase chain reaction is a new non-invasive laboratory study that can help identify infection in cases where the clinical presentation is atypical. Early investigation for EBV in febrile patients with deranged liver function tests and no demonstrable biliary obstruction on imaging can expedite both diagnosis and treatment, thereby avoiding costly or invasive procedures such as liver biopsy.

Keywords: Cholestatic hepatitis, EBV, Epstein-Barr virus

PE-136

Laparoscopic Liver Echinococcectomy

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Aims: Treatment of parasitic liver cysts remains one of the most urgent problems of surgical hepatology. The only way to treat liver echinococcosis is surgery. Drug therapy is ineffective. New perspectives in the treatment of echinococcosis using the possibilities of videoendoscopic surgical interventions-laparoscopic echinococcectomies. The goal is to improve the results of surgical treatment of patients with liver echinococcosis by reducing the traumatism of operations, the frequency of postoperative complications, relapses and the duration of rehabilitation of patients after surgical treatment.

Methods: In the Department of Surgery of the Aktobe Medical Center, in the period from 2013 to 2018 21 laparoscopic operations were performed in patients with liver echinococcosis. Among them were 13 men and 8 women aged 19 to 59 years. Usually used 3 trocars. A trocar with a diameter of 10 mm was introduced into the navel. Additional trocars were administered under laparoscopic control in the subcostal area, at the point directly above the hepatic cyst (10 mm trocar) and along the anterior axillary line (5 mm trocar). After that gauzes were injected into the abdominal cavity moistened with a solution of povidone, which was used to cover the area around the cyst. The same gauzes isolated the subphrenic or subhepatic space depending on the localization of the cyst. The next step was puncture of the cyst with a thick needle with complete suction of the cyst contents with vacuum suction. Then, through the same needle (without removing it from the cyst cavity), a 1% povidone solution was injected into the residual cavity. After exposure for 5 minutes, the entire cyst was aspirated again. The treatment was repeated twice. Then the cyst wall in its most thinned place was opened with electrocoagulation scissors. Excess fibrous capsules with thinned hepatic parenchyma were excised. Shells parasites were removed from the cavity of the cyst using an endocontainer. In a case with bile ducts fissure, we coagulated them with an argon plasma coagulator. The walls of the fibrous capsule were treated with povidone solution. The drainage of the residual cavity was performed by specialized silicone drains. Then gauze moistened with a solution of povidone were removed from the abdominal cavity and the subphrenic or subhepatic space was drained.

Results: Laparoscopic surgery of echinococcal liver cysts was possible in all 22 patients without conversion. The average duration of the operation was 50 ± 12 minutes. No were intraoperative complications. The average length of hospital stay was from 5 to 8 days. No were any complication after operations.

Conclusions: Laparoscopic echinococcectomy can be successfully used in the treatment of liver echinococcosis in patients with superficial echinococcal cysts. The absence of laparotomic incision significantly reduces the time of rehabilitation of patients after surgical treatment.

Keywords: Liver cysts, Laparoscopic surgery

PE-137

A Beneficial and Protective Effect of Carica Papaya Leaves Extract on Rat Peritonitis Model

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Aims: Carica papaya leaves have been used for traditional treatment of dengue fever and have been reported to exhibit an immunomodulatory activity by affecting the level of cytokine production *in vitro* and *in vivo*. The aim of this study was to investigate the antibacterial, anti-inflammatory, and antioxidant activities and probable toxic effects of Carica papaya (CA) in a rat peritonitis model.

Methods: Rats were divided into five groups: (1) Control group, (2) CA group, (3) peritonitis group (P), (4) peritonitis + CA group (P + CA), and (5) peritonitis + antibiotherapy group (P + Ab). Ultrafiltration (UF) rates were determined and colony and leukocyte counts were calculated in the dialysate. Glucose, blood urea nitrogen (BUN), creatinine levels, and alanine transaminase (ALT) activities were studied in blood. Glucose, interleukins (IL-1β, IL-6), and prostaglandin E2 (PGE2) were studied in dialysate and peritoneal tissue for the assessment of the anti-inflammatory effect. Copper/zinc superoxide dismutase (Cu, Zn-SOD), malondialdehyde (MDA), and nitric oxide (NO) were also investigated in peritoneal tissue.

Results: Carica papaya increased the UF rate and lowered leukocyte numbers in the peritonitis group. There was no significant difference in blood and dialysate glucose, BUN, creatinine levels and ALT activity among control and AV groups. AV decreased IL-1β, IL-6 and PGE2 in peritonitis, showing good anti-inflammatory effect. AV showed antioxidant effect on the chosen antioxidant parameters Cu, Zn-SOD, MDA, and NO.

Conclusions: It was concluded that, Carica papaya leaves extract might be used in peritonitis for its probable UF increasing, anti-inflammatory, and antioxidant effects.

Keywords: Rat peritonitis model, Carica papaya leaves, Ultrafiltration, Dialysate glucose

PE-138

Hepatological Profile during Visceral Leishmaniasis

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Aims: We have evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with $3x10^7$ parasites via-intra-cardiac route.

Methods: Mice were treated with anti CD2 adjunct SAG sub-cutaneously twice a week for 4 weeks. Assessment for measurement of weight, spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments.

Results: The combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy ($P = 0.298$) but CD2 treatment even alone significantly influenced IFN-γ production than either SAG treatment ($P = 0.045$) or with CD2 adjunct SAG treatment ($P = 0.005$) in Ld-S strain as well as in Ld-R strain. The super-oxide generation began enhancing very early on day 10 after SAG treatment with CD2 during which SAG action was at minimum. Unlike SAG treatment, treatment of SAG with CD2 also led to production of nitric oxide and TNF-α, resulting in resulting in most effective clearance of L. donovani from infected macrophages.

Conclusions: Our results indicate that CD2 which can boost up a protective Th1 response which can protect liver from further detoriation during Visceral Leishmaniasis infection.

Keywords: Visceral Leishmaniasis, Immunetherapy, CD2, Liver

PE-139

Assessment of Liver Function among Dengue Patients

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Aims: To assess the liver function to evaluate the effect of dengue virus infection by doing liver function test (LFT) and also to understand the impact of dengue infection in different age groups including males and females.

Methods: This prospective study was conducted on serologically confirmed dengue patients (n = 69) from September to November 2018 at A.C.S medical college & hospital (ACSMC&H), Chennai, India. Blood samples were collected and analysed for LFT which includes Total protein, Albumin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase in fully automated Erba XL 200 machine.

Results: The Study group classified to three different groups which is Group 1 (≤30yrs) (n = 40) mean age (22.4 ± 4.3), group 2 (31-50yrs) (n = 19) mean age (40.8 ± 4.8), group 3 (>50yrs) (n = 10) mean age (60.5 ± 8.4). One way anova showed, Total protein, Albumin, and Alanine aminotransferase are statistically significant ($P < 0.05$) in all the study groups.

Conclusions: Important problem in adult patients with Dengue fever is Liver injury but clinical manifestations of liver involvement is not common and it is the major contributing factor in morbidity and mortality of patients with Dengue fever hence the monitoring of liver function is so important especially in elderly people. Total protein, Albumin and Alanine aminotransferase used as early marker to assess the severity of the disease in elderly people.

Keywords: Dengue, Liver function test, Adult population

PE-140

HDV Viral Load Related Liver Fibrosis Patients Clinical Evaluation Based on M2BPGi Level in Serum

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Aims: HBV-HDV coinfection which significantly increases the risk of developing liver cirrhosis and hepatocellular carcinoma (HCC), in Mongolia. HDV-related HCC is understudied, the underlying biological mechanisms associated with liver cancer remains unclear. Mac-2 Binding Protein Glycosylation isomer (M2BPGi) is a novel serological glyco-biomarker for staging liver fibrosis and cirrhosis. We investigate to evaluate the efficiency of serum M2BPGi with chronic hepatitis D infection.

Methods: Serum M2BPGi levels were evaluated in 50 patients with chronic hepatitis D and 25 healthy controls who underwent the hepatologist control in our institution were enrolled in this study. HDV viral load and M2BPGi, PIVKA II level in serum both groups were examined using real time reverse transcription-polymerase chain reaction and ELISA immunoassay. The patients were divided into two groups: high and low groups, based on the HDV viral load. We compared the clinicopathological factors between the high expression and low groups.

Results: M2BPGi serum level was in between healthy controls (0.8 ± 0.49) and hepatitis D patients (6.04 ± 5.8). M2BPGi concentrations also was between in HDV high viral load group 10.8 ± 7.1 (>200 IU/mL, n = 40), HDV low viral load group 1.3 ± 1.4 (<200 IU/mL, n = 10). In the univariate analysis, serum alanine aminotranferase, aspartate aminotranferase, PIVKA II and M2BPGi were determined as the significant risk factors of HDV viral load. Compared with other non-invasive markers, M2BPGi had the greatest specificity for diagnosing cirrhosis and cirrhosis in hepatitis D patients.

Conclusions: Serum M2BPGi could be a non-invasive, predictive new biomarkers for liver fibrosis, cirrhosis and progression of HCC among HDV infected patients.

PE-141

Liver Tuberculosis

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Aims: Tuberculosis is a disease of third world countries but infact no country is immune of it. This disease affects almost all parts of the body. Early recognition is very important. Liver rarely presents with tuberculosis. It has to be differentiated from non tuberculosis liver abscess and fibrolamellar variety of hepatocellular Carcinoma. If it is recognized early then it can be treated with medicine but some times it requires biopsy to confirm the disease. It usually presents with fever and weight loss. In young age hepatic lesions may not be liver cancer and they should be differentiated from the non cancerous lesions.
Methods: A 26 years old female was presented in emergency department for pain abdomen in the epigastric region. She had fever which was high grade for last few weeks. It was associated with off and on nausea and vomiting, Her lab tests were not significant but radiological reports confirmed lesions in the segment 5 and 6. It was found to be the liver tuberculosis after biopsy.
Results: Antituberculosis therapy for 9 months is very good for the treatment of liver tuberculosis if it is recognized early.

Conclusions: Many times hepatic lesions resembles the malignancy. In this case we had noticed that all the history and radiological investigations were in favour of fibrolamellar variety of hepatocellular carcinoma. In these cases probably liver biopsy play a vital role to manage the disease.

NAFLD, Basic

PE-142

Hepatocyte-Targeted shNLRP3 Nanobiologics Facilitated Local Suppression of NLRP3 Inflammasome in the Liver and Reduced Nonalcoholic Steatohepatitis

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Aims: Emerging evidences have indicated that excessive activation of NOD-like receptor protein 3 (NLRP3) inflammasome triggered by toxic lipids promotes the pathogenesis of nonalcoholic steatohepatitis (NASH). Blockade of NLRP3 inflammasome reduces liver inflammation and fibrosis, but initiates gut microbial dysbiosis that drives NASH progression, which should be attributed to the different functions of NLRP3 inflammasome in different organs. Thus, hepatocyte-targeted delivery therapeutics that allows the local suppression of NLRP3 inflammasome in the liver but devoid of microbial dysbiosis is urgently needed for optimal control of NASH.
Methods: Taking advantage of hepatocyte-specific expression of asialoglycoprotein receptor (ASGPR) and the strong affinity of ASGPR for galactose, we developed galactosylated nanobiologics for hepatocyte-targeted suppression of NLRP3 inflammasome. The therapeutic gene pGPU6-shNLRP3 is encapsulated into closed vesicles produced by DOTAP and cholesterol for Nano-shNLRP3 nanobiologics. DSPE was functioned with galactose via PEG to form DSPE-PEG-Galactose, which was post-inserted into phospholipid bilayer of Nano-shNLRP3 to develop Galactose-Nano-shNLRP3 nanobiologics for hepatocyte-targeting. Moreover, hepatocyte-specificity, distribution, safety and therapeutic efficacy of these nanobiologics were also evaluated.
Results: The data presented here showed that Galactose-Nano-shNLRP3 nanobiologics were specifically internalized by hepatocyte cell lines via the endocytosis mediated by ASGPR. *In vivo* distribution studies further confirmed the rapid and extensive hepatic accumulation of Galactose-Nano-shNLRP3. The evaluated levels of shNLRP3 in the hepatocytes by Galactose-Nano-shNLRP3 contributed to the hepatic-specific suppression of NLRP3 and efficient prevention of liver inflammation and steatosis. Meanwhile, Galactose-Nano-shNLRP3 were not immunotoxic and did not induce gut dysbiosis.
Conclusions: This work illustrated the potential of Galactose-Nano-shNLRP3 nanobiologics as a promising hepatocyte-targeted therapeutics against NASH through facilitating the local suppression of NLRP3 inflammasome in the liver.
Keywords: NLRP3 inflammasome, Nonalcoholic steatohepatitis, Hepatocyte-targeted, Nanobiologics

PE-143

NAFLD Screening among Newly Diagnosed Diabetics in Dornod Province, Mongolia

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Aims: Prevalence of diabetics increased dramatically during last two decades in Mongolia. The nationwide studies reported a significant increase in prevalence; 3.1%, 6.5% in 1999, 2010, respectively. Non-alcoholic fatty liver disease (NAFLD) is a chronic medical condition strongly associated with diabetes. Therefore, we aimed to study NAFLD risk among newly diagnosed diabetics in eastern province Dornod, Mongolia.
Methods: We used cross-sectional study design to screen NAFLD

among newly diagnosed type 2 diabetic patients in Choibalsan, Dornod province. Thirty-one subjects who denied alcohol consumption were recruited from August to December 2018. We collected anthropometric data, clinical chemistry data including glucose metabolism panel, albumin, liver enzymes, lipids, complete blood cell analysis for NAFLD Fibrosis score and abdominal ultrasound. Chi-square, T-test, ANOVA and other statistical methods were used.

Results: Among participants, four (12.9%) subjects had significant fibrosis (F3-F4 fibrosis), 16 (51.6%) were in borderline or indeterminable. We observed a significant difference in serum ALT level (76.00 ± 30.31 vs 28.51 ± 3.43, P = 0.002) and platelet count (277.04 ± 17.34 vs154.35 ± 21.56,P = 0.013)between the subject with significant fibrosis and fibrosis indeterminable or absent subjects. In addition, ALT level was significantly correlated with only serum triglyceride among lipid panels (r = 0.542, p = 0.002). Liver sonography changes including hepatomegaly (P = 0.110) and hyper-echogenic appearance (P = 0.294) were not associated with NAFLD. We have not observed any difference in age and sex subgroups (P > 0.05).

Conclusions: We have demonstrated non-invasive NAFLD screening among new diabetics in resource limited rural area of Mongolia. Significant fibrosis (F3-F4) was present in at least one eighth of newly diagnosed diabetics. Serum ALT level and platelet count tests are available in rural areas and should be considered for screening among clinicians. Abdominal ultrasound did not reveal significant clinical importance in our study.

Keywords: NAFLD, Diabetic

PE-144

Ameliorating Liver Fibrosis Using the Secretome Released from miR-122 Transfected Adipose-Derived Stem Cells in an Animal Model

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Aims: Recently, the exclusive use of mesenchymal stem cell (MSC)-secreted molecules, named as the secretome, rather than cells has been evaluated for overcoming the limitations of cell-based therapy while maintaining its advantages. In this study, we were intended to determine the therapeutic potential of secretome released from miR-122 transfected ASCs.

Methods: We collected the secretory materials released from ASCs that had been transfected with antifibrotic miR-122 (MCM), and compared their antifibrotic effects with naïve secretome (CM). MCM and CM were intravenously administered to the mouse model of thioacetamide-induced liver fibrosis, and their therapeutic potentials were compared.

Results: MCM infusion provided higher therapeutic potential in terms of (a) reducing the collagen content in the liver, (b) inhibiting the proinflammatory cytokines, and (c) reducing the abnormally elevated liver enzymes than did the infusion of naïve secretome. The proteomic analysis of MCM also indicated that the contents of antifibrotic proteins were significantly elevated than naïve secretome.

Conclusions: We thus could conclude that the secretome released from miR-122 transfected ASCs has higher antifibrotic and anti-inflammatory properties than naïve secretome. Because miR-122 transfection into ASCs provides a specific way of potentiating antifibrotic properties of ASC-secreteome, it could be considered as an upgraded way of reinforcing the secretome effectiveness.

PE-145

Association of Coffee and Caffeine Consumption with Fatty Liver Disease, Nonalcoholic Steatohepatitis, and Degree of Hepatic Fibrosis

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Aims: Coffee caffeine consumption (CC) is associated with reduced hepatic fibrosis in patients with chronic liver diseases, such as hepatitis C. The association of CC with nonalcoholic fatty liver disease (NAFLD) has not been established. The aim of this study was to correlate CC with the prevalence and severity of NAFLD.

Methods: Patients involved in a previously published NAFLD prevalence study, as well as additional NASH patients identified in the Hepatology Center of Almaty, were queried about their caffeine intake. A validated questionnaire for CC was utilized to assess for a relationship between caffeine and four groups: ultrasound negative (controls), bland steatosis/not-NASH, NASH stage 0-1, and NASH stage 2-4. A total of 306 patients responded to the CC questionnaire. Average milligrams of total caffeine/coffee CC per day in controls, bland steatosis/not-NASH, NASH stage 0-1, and NASH stage 2-4 were 307/228, 229/160, 351/255, and 252/152, respectively. When comparing patients with bland steatosis/not-NASH to those with NASH stage 0-1, there was a significant difference in CC between the two groups (P = 0.005). Additionally, when comparing patients with NASH stage 0-1 to those with NASH stage 2-4, there was a significant difference in coffee CC (P = 0.016).

Results: Spearman's rank correlation analysis further supported a negative relationship between coffee CC and hepatic fibrosis (r = -0.215; P = 0.035).

Conclusions: Coffee CC is associated with a significant reduction in risk of fibrosis among NASH patients.

Keywords: Hepatic fibrosis, Chronic liver diseases, Hepatitis C, Coffee caffeine consumption

PE-146

Chorionic-Plate-Derived Mesenchymal Stem Cells Attenuate Hepatic Steatosis via Restoration of Mitochondrial Function

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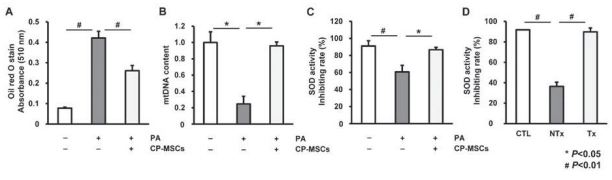
Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, but its pathophysiology is not fully understood due to complexity of the mechanisms involved in the disease. Moreover, the pharmacological therapy for NAFLD is not yet available. We investigated the effects of chorionic-plate-derived mesenchymal stem cells (CP-MSCs) on hepatic steatosis and mitochondrial function.

Methods: HepG2 cells were treated with palmitic acid (PA), and then co-cultured with CP-MSCs. Intracellular lipid accumulation was assessed by oil red O staining and mitochondrial mass was measured by staining mitochondria and quantifying mitochondrial DNA (mtDNA). Male C57BL/6J mice were chronically fed with high-fat diet (HFD). At week 29, mice were injected with either phosphate-buffered saline (NTx) or CP-MSCs (Tx; 1×10^6 cells, 8–10 passages). Four weeks later, liver histology and function were assessed.

Results: PA-induced intracellular lipid accumulation was attenuated when co-cultured with CP-MSCs (Fig. 1A). The mitochondrial mass was reduced by PA treatment and then was restored following co-culture with CP-MSCs (Fig. 1B). Expression of genes involved in regulation of mitochondrial function, such as PGC1 and sirtuins, was dynamically changed by PA treatment and CP-MSC co-culture. Cellular reactive oxygen species production was increased by PA treatment and then was attenuated after CP-MSC co-culture. The activity of superoxide dismutases (SODs) was suppressed by PA treatment and was restored by co-culture with CP-MSCs (Fig. 1C). Severe hepatic steatosis in HFD-fed mice was ameliorated following transplantation of CP-MSCs. Decreased activity of SODs was reverted to near the levels of normal diet-fed mice after transplantation of CP-MSCs (Fig. 1D).

Figure 1



Conclusions: Hepatic steatosis and mitochondrial dysfunction in NAFLD can be ameliorated by transplantation of CP-MSCs. Our study findings suggest the therapeutic potential of CP-MSCs in NAFLD and help understanding alterations in hepatic lipid metabolism which may be restored by CP-MSC transplantation.

Keywords: NAFLD, Stem cells, CP-MSCs, Mitochondria, ROS, SOD

PE-147

Oxidized Lipoproteins Induce Accumulation of Oxidized Triglycerides and Cholesteryl Ester in Lipid Droplets of Liver Cell

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Aims: Non-alcoholic fatty liver disease (NAFLD) is typically characterized by the excessive accumulation of lipid droplets (LD) in the liver and is associated with the presence of metabolic disorders such as diabetes mellitus, obesity, dyslipidemia, hypertension, and oxidative stress. Oxidative modification of LD can induce inflammatory events that can potentially progress to severe liver disease. Since the oxidatively modified lipoproteins carry considerable amount of oxidized lipid that can be taken up by the liver. Therefore, the present study is designed to investigate the role of oxidized lipoproteins in the formation of LD rich in oxidized lipids in liver cells.

Methods: A fasting EDTA blood sample was collected from a healthy human volunteer to isolate VLDL, IDL, LDL and. Oxidized lipoproteins (oxVLDL, oxIDL, oxLDL, oxHDL) were prepared by incubating the lipoprotein fraction with Cu^{2+} for 2, 4 and 8 hours. LD in the HepG2 cells were induced by incubating cells in DMEM medium supplemented with 0.2 mM of each oleic and linolenic acid. Then the cells were treated with the oxidized lipoproteins and incubated for 24 hours. Single LD sample was isolated from the cells using 3D mobile manipulator under brightfield invert microscope. The extracted LD from the cells were analyzed with LTQ Orbitrap mass spectrometry equipped with nano-electrospray ionization.

Results: The amount of triglyceride hydroperoxides (TGOOH) in LD treated with native VLDL and IDL less than 0.5%. The relative amount of TGOOH in LD depends on the degree of oxidation of VLDL and IDL. As high as 5% of TG were oxidized in the cells treated with oxVLDL oxidized for 8 hr. Treatment of cells with oxLDL and oxHDL is associated with a significant increase in the concentration of cholesteryl ester hydroperoxides (CEOOH) in LD.

Conclusions: TGOOH and CEOOH in oxidized lipoproteins can be incorporated in LD in liver cells. The incorporation depends on the degree of oxidation. Accumulation of such oxidized lipid molecules in the LD may be associated with the pathological process.

Keywords: Lipid, Lipid droplet, Non-alcoholic liver disease, Oxidized lipids

PE-148

Could Cholecystectomy Facilitate or Augment Non-Alcoholic Fatty Liver Disease? Association or Causal Relationship?

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Aims: Several clinical data strongly suggest an association between cholecystectomy (XGB) and prevalence of non-alcoholic fatty liver disease (NAFLD). But the exact mechanism is unknown, and its causal relationship is also unclear. We tried to investigate the causal relationship between XGB and NAFLD.

Methods: Sham operation and cholecystectomy was performed in two different settings (normal diet condition (study I), and 60% high fat diet (study II)), respectively. Repeated liver biopsy without sacrifice was done at 1, 2, and 4 months. Liver histology, biochemistry, PCR, and western blot for metabolic parameters were compared to sham operation group. Quantitation of bile-acid composition was determined using UPLC-ESI-QTOFMS. The concentration of metabolites was quantified by multiple reaction-monitoring mass spectrometry based on standard curves using authentic standards.

Results: In study 1 (sham vs. cholecystectomy in normal diet), there was no difference in body weight and liver chemistry (ALT, AST, triglyceride and cholesterol levels) at 1, 2, and 4 months. NAFLD activity score (NAS) including hepatic steatosis, inflammation, and ballooning changes was not different between sham and XGB group, except at early stage. Immunohistochemical stain for hepatocyte apoptosis (CK-18, and TUNEL stain), and qPCR for hepatic apoptosis and fat de novo synthesis pathway were not different between control and XGB model in normal diet condition. In study 2 (sham vs. cholecystectomy in 60% high fat diet for 6 months), there were no differences between control and XGB model in NAFLD condition regarding body weight, liver histology, blood chemistry, and molecular study. Hepatic concentration of LCA, CA, UDCA, CDCA, and DCA in control and XGB model was not different at different conditions (normal chow and high fat) at 1, 2, and 4 months.

Conclusions: Cholecystectomy can cause transient liver injury at early stage, but cholecystectomy did not cause and facilitate fat accumulation as well as hepatic inflammation in both normal and obese condition.

Keywords: NAFLD, Cholecystectomy, Cell death

PE-149

Nonalcoholic Fatty Liver Disease in Severely Obese Adolescent and Adult Patients

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Aims: Nonalcoholic fatty liver disease (NAFLD) is increasingly an indication for liver transplantation in adults. While severe obesity (SO, BMI ≥40 kg m(-2)) in adults is long standing, it is recent in duration in adolescents. With adolescent obesity on the rise, NAFLD is becoming the most frequent liver disease in adolescents. The hypothesis that SO adolescents and adults have different severity of NAFLD because of longer duration of obesity in SO adults was tested.

Methods: Preoperative clinical data, NAFLD activity and NASH (Nonalcoholic steatohepatitis) scores from intraoperative liver biopsies were extracted from a prospective database of consecutively operated SO adolescents and adults (n = 24 each). Fasting preoperative serum inflammatory mediators were evaluated by ELISA.

Results: Other than age, baseline BMI, ethnicity and gender distribution, the incidence and extent of dyslipidemia, hypertension, and metabolic syndrome were comparable between groups. Histologic scores for steatosis and inflammation were similar. Adolescents have significantly higher NASH incidence, hepatocyte injury scores and fibrosis. This was associated with higher serum C-reactive protein and sCD14 levels.

Conclusions: For comparable BMI and metabolic profile, SO adolescents have more advanced liver damage, more severe systemic inflammation, suggesting differences in NAFLD etiologies and more aggressive disease progression in the young obese population.

Keywords: NAFLD, Liver transplantation, Nonalcoholic steatohepatitis, C-reactive protein

PE-150

Effects of Lactobacillus and Bifidobacterium Strains on Gut Liver Axis in NAFLD Mouse

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Aims: Nonalcoholic fatty liver disease (NAFLD) is major global public health problem and its incidence is continually increasing. In our previous study, treatment with *Lactobacillus bulgaricus* (LB), *L. helveticus* (LH), *Bifidobacterium longum* (BL) and *B. breve* (BB) improved Western died induced NAFLD. We aimed to evaluate the effect of combination therapy with *Lactobacillus* and *Bifidobacterium* strains on gut liver axis in NAFLD mouse.

Methods: We used 6-week aged C57BL/6 mice and divided 6 groups (n = 5/group; normal diet, Western diet, and 4 probiotics test groups (LB+BL, LB+BB, LH+BL, and LH+BB groups, 10^9 CFU/g for 8 weeks). We compared liver/body weight (L/B) ratio, liver histology (steatosis and inflammation), liver enzymes and inflammatory cytokine (tumor necrosis factor [TNF]-α and interleukin [IL]-1β).

Results: In the analysis of L/B ratio (%), LB+BL (5.1 ± 0.2), LB+BB (4.7 ± 0.5), and LH+BB (5.2 ± 0.5) groups showed signif-

icant improvement compared with Western control group (6.3 ± 0.9, $P < 0.05$). All combination groups showed significant improvement in steatosis/inflammation (Western diet [2.6 ± 0.5/2.0 ± 0.1], LB+BL [2.0 ± 0.0/1.0 ± 0.0], LB+BB [1.4 ± 0.5/1.0 ± 0.0], LH+BL [1.8 ± 0.4/1.0 ± 0.0], and LH+BB [1.4 ± 0.5/1.0 ± 0.0], $P < 0.05$). LB+BB group showed reduction in alanine transaminase level (57 ± 32 IU/L) compared with Western diet group (126 ± 57 IU/L). Elevated TNF-α/IL-1β levels in Western diet group (12 ± 3/12 ± 3 pg/ml) were significantly reduced in LB+BL (9 ± 3/12 ± 3 pg/ml), LB+BB (10 ± 4 pg/ml), LH+BL (8 ± 3 pg/ml) and LH+BB (11 ± 3 pg/ml) groups ($P < 0.05$).

Conclusions: Probiotics treatment with *Lactobacillus* and *Bifidobacterium* strains improved steatohepatitis by modulating inflammatory pathway in gut-liver axis of NAFLD. Further studies such as clinical trials are need in the future for the evaluation of mechanism and clinical application.

Keywords: Nonalcoholic fatty liver disease (NAFLD), Western diet, Lactobacillus bulgaricus (LB), Lactobacillus helveticus (LH), Bifidobacterium longum (BL), Bifidobacterium breve (BB)

PE-151

Modulation of Gut-Microbiome by Probiotics Ameliorates Progression of Non-Alcoholic Fatty Liver Disease

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Aims: Targeting gut-liver axis by modulating gut-microbiome can be a promising treatment in non-alcoholic fatty liver disease (NAFLD). The aim of study was to evaluate the effect of single and combinations of probiotics in NAFLD mice model.

Methods: We used 6-week male C57BL/6J mice and divided them into 8 groups (n = 10/group; normal, Western, and 7 Western-probiotics groups [10^9 CFU/g, for 8 weeks]). The strains used were *Lactobacillus bulgaricus, L. casei, L. helveticus, Pediococcus pentosaceus* KID7 and 3 combinations (1: *L. casei+L. helveticus*, 2: *L. casei+L. helveticus+P. pentosaceus* KID7, and 3: *L. casei+L. helveticus+L. bulgaricus*). Liver/body weight ratio, serum analysis, cytokines, steatosis/inflammation scores, and stool microbiome analysis by 16S rRNA-based sequencing were examined.

Results: *L. bulgaricus* (5.05 ± 0.46), *L. casei* (5.67 ± 1.07), *L. helveticus* (5.15 ± 0.38), *P. pentosaceus* KID7 (5.47 ± 0.48), combination 1 (4.24 ± 0.63), and 2 groups (4.80 ± 0.65) showed significant reduction in liver/body weight ratio compared with the Western group (6.16 ± 0.56) ($P < 0.001$). In the comparison of cholesterol, steatosis/inflammation score, all probiotics except *L. casei* revealed an improvement ($P < 0.05$). Elevated level of tumor necrosis factor-α and interleukin-1β in Western group (65.8 ± 7.9 and 163.8 ± 12.2 pg/ml) was significantly reduced in *L. bulgaricus* (24.2 ± 1.01 and 58.9 ± 15.3 pg/ml), *L. casei* (35.6 ± 2.1 and 62.9 ± 6.0 pg/ml), *L. helveticus* (43.4 ± 3.2 and 53.6 ± 7.5 pg/ml), *P. pentosaceus* KID7 (22.9 ± 3.4 and 59.7±12.2 pg/ml) groups, respectively ($P < 0.01$). In the analysis of stool microbiome, elevated *Fermicutes/Bacteroidetes* ratio in western group (47.1) was decreased in *L. bulgaricus* (14.5), *L. helveticus* (3.0), and *P. pentosaceus* KID7 (13.3) groups.

Conclusions: Probiotics treatment with *L. bulgaricus*, *L. casei*, *L. helveticus*, and *P. pentosaceus* KID7 improved steatohepatitis by modulating gut microbiota composition and inflammatory pathway in gut-liver axis of NAFLD.

Keywords: NAFLD, Gut liver axis, Liver function, Probiotics

PE-152

Self-Management of Patients with Non-Alcoholic Fatty Liver Disease: A Focus Group Interview Study

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Aims: The prevalence of non-alcoholic fatty liver disease (NAFLD) has been increased in the world. Self-management including life style modification, diet, and exercise may be important to improve health outcomes in patients with NAFLD. However, few studies have identified and assessed the characteristics of self-management in this population. The purpose of this study was to explore the experiences of patients regarding NAFLD self-management.

Methods: A focus group interview study with a descriptive design was applied. From November to December 2018, 12 subjects were recruited from outpatient clinic of the liver center, in Severance hospital, Seoul, Korea. Major questions were the follows: "What do you do to manage your NAFLD?", "What are the difficulties in managing NAFLD?", "What do you want healthcare providers to do for your NAFLD?" Interviews were all audio-recorded and transcribed, and transcripts were analyzed using qualitative content analysis.

Results: Five of 12 participants were men (42%) and the mean age was 54 years old. The mean score of length of diagnosis was 8.9 years. Four categories were emerged as follows: (1) insufficient health education related to managing NAFLD, (2) obtaining health information from various sources, (3) lack of competence in self-management, (4) high demands of tailored health education by healthcare providers. The participants described that self-management was difficult for them because specified information was not provided, even though they received some medical directions from healthcare providers. As a result, it seemed that participants get unverified health information from various sources including internet, TV and people other than healthcare providers. Moreover, self-management in NAFLD involves modification of lifestyle, which is more complex

and difficult than following medical instructions such as taking medication or visiting doctor's office for follow-ups.
Conclusions: The present findings of this study revealed that patients with NAFLD may have low competences of self-management. Hence, healthcare providers should develop the tailored interventions to enhance competence of self-management for patients with NAFLD.
Keywords: Self-management, Non-alcoholic fatty liver disease, Focus group interview, Health education

PE-153

Dipeptidyl Peptidase-IV Inhibitors and Antioxidant Properties of Alkaloids Rich Fraction of Withania Somnifera Improve Liver Dysfunction in Type 2 Diabetic Mellitus

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Aims: A novel approach in the treatment of T2DM, based on incretin hormone which regulated by Dipeptidyl peptidase–IV (DPP-IV). Dipeptidyl peptidase-IV inhibitor (DPP-IV) of *Withania somnifera* (WS) might have pleiotropic effect due to DPP-IV receptor present on various tissues, including liver. We examined whether DPP-IV inhibitors effect on non-alcoholic fatty liver function in Type 2 Diabetic Mellitus (T2DM) along with antioxidant properties in rat model.
Methods: T2DM model was induced in wistar rats with high sucrose diet along with dexamethasone. Biochemical, toxicology and histology variable were evaluated between all the groups, apart from serum DPP-IV inhibition,Insuline, HbA1c, histology of liver tissue were examine. In *ex-vivo*, hepatic lipid peroxidation, erythrocytes haemolysis was performed.
Results: After administration of alkaloids rich fraction of WS, there was a DPP-IV inhibition activity increase in WS (71.39%), as compared to Sitagliptin (91.16%) with significant reduction in levels of glucose, Insulin, HbA1c, TC, TG. DPP-IV inhibitors also reduced the level of aminotransferases i.e SGOT & SGPT and alkaline phosphatase with improvment of liver tissue histology. WS plant extract have showed better antioxidant capacity to protect lipid peroxidation and reduced erythrocytes haemolysis of RBC.
Conclusions: DPP-IV inhibitors improve insulin, HbA1c sensitivity and help to improve the liver dysfunction in T2DM.
Keywords: Dipeptidyl peptidase-IV, Lipid peroxidation, Aminotransferases, Diabetic mellitus

PE-154

Probiotics Affect Adipose Tissue to Reduce NAFLD

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Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, comprises a spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis, fibrosis, and cirrhosis. Currently, there are no Food and Drug Administration–approved therapies for NAFLD. Although the molecular mechanisms of probiotics have not been completely elucidated yet, has been shown to be beneficial in NAFLD by the regulation of intestinal microorganisms. The aim of this study is to find how probiotics affect NAFLD.
Methods: Six-week male C57BL/6J mice were used in this study. Mice were randomly assigned to normal diet, Western-diet, and 4 Western diet+probiotics groups (n = 10/group). Used probiotics strains are *Lactobacillus bulgaricus, L. casei, L. helveticus, Pediococcus pentosaceus KID7*. Liver/body weight ratio, and histologic findings (hepatitis and steatosis score) were analyzed. Measurement of serum liver enzyme (ALT, AST), cholesterol and adipokines. Western blotting, Quantitative real-time PCR and Gut microbiota metagenome were analyzed.
Results: In the analysis of liver/body weight ratio, *L. bulgaricus* (5.1 ± 0.5, $P < 0.001$), *L. casei* (5.7 ± 1.0, $P < 0.1$), *L. helveticus* (5.2 ± 0.4, $P < 0.001$), *P. KID7* (5.5 ± 0.5, $P = 0.009$) groups showed significant improvement compared with that of Western group (6.2 ± 0.6). In comparison of histology (hepatitis score/steatosis score), *L. bulgaricus* (0.7 ± 0.7/0.7 ± 0.7, $P < 0.001$), *L. casei* (1.8 ± 0.4/2.1 ± 0.6, $P < 0.001$), *L. helveticus* (1.3 ± 0.5/1.7 ± 0.7, $P < 0.001$) and *P. KID7* (1.3 ± 0.5/1.4 ± 0.5, $P < 0.001$) reveled significant improvement compared with that of Western group (3.1 ± 0.3/2.0 ± 0.0). All strains were effective in improvement of liver enzyme (AST or ALT, $P < 0.05$), except *L. casei*, significantly reduced the level of cholesterol ($P < 0.05$). The expression of RBP4 by western blot was shown that decreased in *L. bulgaricus*, *L. casei*, *L. helveticus* and *P. KID7* as compared with western diets. Also it was confirmed by q-PCR that the expression of mRNA was significantly reduced. Levels of TNF-α, IL6 and IL1β were measured by ELISA in serum and all of them were significantly decreased compared with western diet. Gut microbiome analysis revealed that 8 weeks of western diet resulted in enrichment of Firmicutes and Proteobacteriam Verrucomicrobia in the intestinal microbial community structure at the phylum level and a significant decrease in Bacteroidetes.
Conclusions: We found that probiotics affected intestinal microbial composition and decreased cytokines expressed in adipocytes. Restoration of intestinal microbial composition by probiotics lowers the expression of leptin and RBP4 from adipocytes, which lowers hepatitis by lowering the expression of hepatic cytokines.
Keywords: NAFLD, RBP4, Probiotics, Microbiome

PE-155

The Effect of Orange Water Kefir on Malondialdehyde Level in Liver Tissue of the Hyperlipidemic Rat

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ingtyas[2]

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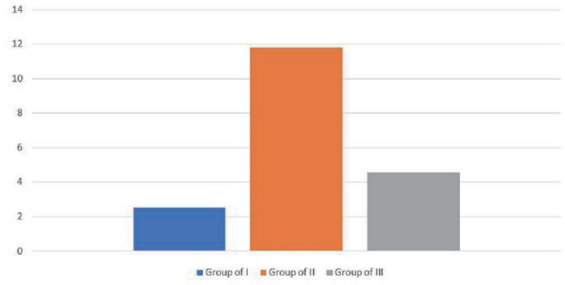
Aims: The liver is an organ that plays an important role in various metabolic processes, including lipid metabolism. The accumulation of excess lipids in liver tissue can increase the level of reactive oxygen species (ROS). It can increase lipid peroxidation that marked by malondialdehyde (MDA) levels in the liver tissue. If this compilation occurs continuously, it will increase the risk of non alcoholic liver disease. The previous research shown water kefir and orange, each has been proven to reduce the MDA level. The aim of this research was to determine the effect of orange water kefir intervention on MDA level in liver tissue of hyperlipidemic rat.

MALONDIALDEHYDE LEVEL OF LIVER TISSUE (nmol/gr)



ANOVA

MDALevel

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	238,021	2	119,011	1146,170	,000
Within Groups	1,246	12	,104		
Total	239,267	14			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: MDALevel

Bonferroni

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
K+	K-	9,28600*	,20380	,000	8,7196	9,8524
	P	7,23800*	,20380	,000	6,6716	7,8044
K-	K+	-9,28600*	,20380	,000	-9,8524	-8,7196
	P	-2,04800*	,20380	,000	-2,6144	-1,4816
P	K+	-7,23800*	,20380	,000	-7,8044	-6,6716
	K-	2,04800*	,20380	,000	1,4816	2,6144

*. The mean difference is significant at the 0.05 level.

Methods: This study used experimental method with post test only control group design. The sample of this study were 15 male rat (Rattus norvegicus) aged 2-3 months and weight 180-250 grams. All groups were acclimatized for one week and fed ad libitum for 8 weeks. Group II and III were given quail egg yolk with dose 5 ml/200 grams of body weight for 4 weeks. For the next 4 weeks, group III was given the orange water kefir with dose of 5 ml/200 grams of body weight. All the intervention were given by the sonde method. Orange water kefir was made in accordance with good manufacturing product (GMP) standards and the procedure to making water kefir. At the end of the study, rats were terminated and the liver organ were examined for MDA level.

Results: Mean of MDA level on each group consecutively were 2.514 ± 0.12268 nmol/dl, 11.8 ± 0.17 nmol/dl, and 4.562 ± 0,12 nmol/dl. The Statistical Analysis with Oneway ANOVA showed significant differences in MDA level beetwen three groups with $P = 0.00$. While, Bonferroni post-hoc test showed significant comparison beetwen these groups with $P = 0.00$.

Conclusions: The intervention of orange water kefir was significantly reduce the MDA level of hyperlipidemic rats ($P < 0.001$).

Keywords: Hyperlipidemia, Malondialdehyde, Orange, Water kefir

PE-156

Lipid Fraction Area of Liver Histology after Intervention with Probiotic Beverage from Date Palm and Kefir Milk in the Hyperlipidemic Rats (Rattus Norvegicus)

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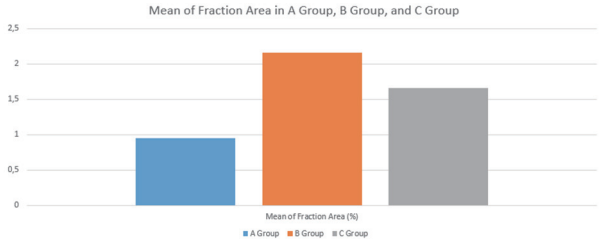
Aims: Hyperlipidimia is a condition that will trigger liver tissue damage and atherosclerosis. Atherogenic hyperlipidemic is often associated with the occurrence of Non Alcoholic Fatty Liver Disease (NAFLD), where the pathological hallmark of NAFLD is characterized by the accumulation of lipids in hepatocytes. Based on previous research, probiotics have been proven to reduce lipid accumulation in the liver. The purpose of this research is to know the effect of probiotic beverage from date palm and kefir milk on the lipid fraction area of liver histology.

Methods: This research used quasi-experimental method with post-test only control group design. Rats were divided into 3 groups (A group, B group, and C group). All groups were given fed *ad libitum* for 8 weeks. Group of B and C were given quail egg yolk in the first 4 weeks with a dose of 5 ml/ 200 grBW. In the second 4 weeks, C group was given a probiotic beverage from date palm and kefir milk. The dose of beverage was 5 ml/ 200 grBW. All intervention were administered to rats with sonde method. At the end of the research, rats were terminated. Liver tissue stained with hematoxylin-eosin. The lipid fraction area was measured with ImageJ application. Data collected and analyzed with statistic software.

Results: All data were expressed as mean ± standard deviation (%). For A group (0.95 ± 0.16), B group (2.16 ± 1.55), and C group (1.66 ± 0.73). One way ANOVA test showed no significant difference after the intervention of probiotic beverage

from date palm and kefir milk on lipid fraction area of liver tissue ($P > 0.05$).

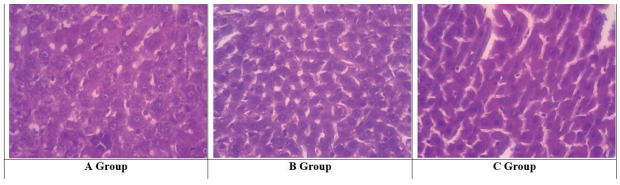


Test Statistics[a,b]

	Fraction_Area
Kruskal-Wallis H	5.161
df	2
Asymp. Sig.	.076

a. Kruskal Wallis Test

b. Grouping Variable: Grup A



Conclusions: There was no significant difference of lipid fraction area of liver tissue in the hyperlipidemic rat model after intervention with probiotic beverage consist of date palm and kefir milk.

Keywords: Hyperlipidemia, Fatty liver, Lipid fraction area, Kefir milk, Date palm

PE-157

EWSR1, a Potential Therapeutic Target in Non-Alcoholic Fatty Liver Disease

Gil Won Lee[1], Wonhee Hur[1], Sung Min Kim[1], Dong Jun Park[1], Byung-Yoon Kang[1], Jaegyoon Ahn[2], Sean Bong Lee[3], and Seung Kew Yoon[1*]

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Aims: Non-alcoholic fatty liver disease (NAFLD) caused by an accumulation of lipid in the liver is a very common chronic disease worldwide. Although considerable progress has been made recently in illuminating the pathogenesis of NAFLD, it remains unclear which mechanisms are associated with the progression of NAFLD. Previous studies have shown that Ewing sarcoma breakpoint region 1 (EWSR1) is an RNA binding protein involved in transcription and splicing, in maintaining mitochondria homeostasis. This study investigated the potential roles of EWSR1 in the progression of NAFLD.

Methods: Expression of EWSR1 was analyzed in the liver of NAFLD-induced mice fed with high-fat diet (HFD). Immunofluorescence assay was used to detect lipid accumulation in Oleic acid (OA)-induced mouse embryonic fibroblast (MEF) EWSR1 knock out cell. cDNA microarray analysis of EWSR1 knock out (KO) mouse liver identified genes in lipid biosynthetic and growth control pathways.

Results: The EWSR1 expression was increased in HFD-induced NAFLD mice compared with normal diet mice. Lipid accumulation was increased OA-induced EWSR1 KO MEF cell than MEF cell. Microarray expression profiling revealed specific genes, which are mostly involved in fatty acid β-oxidation, glucose and insulin sensitivity were differentially expressed in the liver of EWSR1 KO mice. These results demonstrated, for the first time, that attenuated oxidation-reduction and fatty acid β-oxidation in steatotic liver is associated with an impaired biological activity of EWSR1.

Conclusions: These results suggest that EWSR1 expression may act as a key regulator for controlling such things as lipid metabolism in NAFLD, as well as may overcome limitations by improving problems with existing research and development treatments about NAFLD. Further Investigation of the role of EWSR1 in NAFLD pathogenic procession is underway in EWSR1 deficient mice fed HFD.

Supported by grants of the Basic Science Research Program through NRF, NO. 2016R1D1A1B03931395 and BK21.

Keywords: Non-alcoholic fatty liver disease, Ewing sarcoma breakpoint region 1, Insulin metabolism, Lipid metabolism

PE-158

CJ-14199, a Novel Ileal Bile Acid Transporter Inhibitor for Non-Alcoholic Steatohepatitis

Jin Woo Jung[1], Hyungjin Jun[1], Dong-Hyun Kim[1], Keun-Ho Lee[1], Byoung Soo Kim[2], Dong-Kyu Kim[1], Soo-Jin Kim[1], Byoung-Seok Moon[1], Shin-Young Ryu[1]

[1]R&D Center, CJ HealthCare Corporation, [2]Molecular Imaging Research Center, Korea Institute of Radiological & Medical Sciences, Korea

Aims: In the present study, we demonstrate the *in vitro* and *in vivo* pharmacological properties of CJ-14199 and the efficacy of CJ-14199 in mouse NASH models.

Methods: *In vitro* [^{14}C]taurocholate uptake inhibition assay was performed using hIBAT- or hLBAT (Liver BAT)-overexpressing cell lines. *In vivo* pharmacological properties of CJ-14199 were determined by measuring fecal bile acid and plasma C4 in normal ICR mice. *In vivo* efficacy of CJ-14199 was evaluated by

NAS (Non-alcoholic fatty liver disease Activity Score) and fibrosis area in mouse NASH models. Quantitative whole-body autoradiography (QWBA), absolute bioavailability, and fecal recovery studies were performed in rats using [^{14}C]CJ-14199.

Results: CJ-14199 inhibited the [^{14}C]taurocholate uptake in IBAT- or LBAT-overexpressing cells with IC_{50} of 1.83 and 7200 nM, respectively, suggesting ~4000 fold selectivity for IBAT over LBAT. In normal ICR mice, oral administration of CJ-14199 caused an increase of fecal bile acid in a dose-dependent manner, with the increase of plasma C4. In mouse NASH models, CJ-14199 induced significant reduction in NAS and prevented progression of fibrosis. From the QWBA, absolute bioavailability, and fecal recovery studies using [^{14}C]CJ-14199, CJ-14199 exhibited optimal pharmacokinetics properties as a minimally absorbed locally acting gastrointestinal drugs.

Conclusions: CJ-14199 is a highly selective IBAT inhibitor with the characteristics of locally acting gastrointestinal drugs. The robust efficacy in NASH animal models suggests that CJ-14199 has the potential as a new NASH therapeutics.

Keywords: Non-alcoholic steatohepatitis, NASH, Ileal bile acid transporter inhibitor, IBAT, CJ-14199

NAFLD, Clinical

PE-159

Comparison of the Efficacy of Ursodeoxycholic Acid (UDCA) versus Vitamin E plus Vitamin C in Non-Diabetic Patients with Nonalcoholic Steatohepatitis (NASH)

Tatia Khachide[1,2], Gocha Barbakadze[1,2], Manana Jebashvili[1], Gela Sulaberidze[1], Koba Burnadze[2]

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Aims: Nonalcoholic steatohepatitis (NASH) is a frequent liver disease that can progress to cirrhosis and for which effective therapy is still lacking. Despite an important role of oxidative stress in the pathogenesis of NASH, antioxidant approaches have not been investigated sufficiently. The aim of the study was to compare ursodeoxycholic acid (UDCA) versus vitamin E plus vitamin C in non-diabetic patients with nonalcoholic steatohepatitis.

Methods: Patients with elevated aminotransferase levels and drinking, less than 40g alcohol/week with NASH diagnose were randomly assigned to receive either UDCA 15 mg/per kg/day (group A) or vitamin E 800 mg/day plus vitamin C 500 mg/day (group B) for 12 months and control group, which did not receive any medical treatment. Lifestyle modification was advised to all groups. The primary study end point was improvement in aminotransaminase levels, secondary end points were improvement in steatosis score and improvement in fibrosis score.

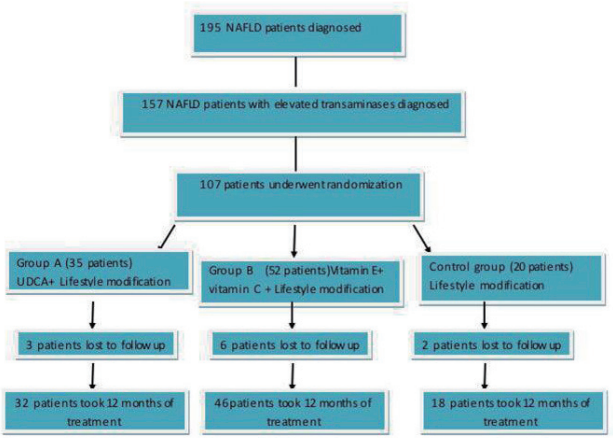

Figure1. The trial profile of participants who completed follow up

Results: 107 patients were included 35 in the group A, 52 in the group B and 20 in control group, 11 patients dropped out, non because of side effects. Baseline characteristics were not significantly different between groups. After 12 months treatment with vitamin E plus C, as compared with UDCA, was associated with a significant reduction of mean alanine aminotransferase (ALT) levels. Similarly, there was significant reduction of both mean steatosis score and fibrosis score.

Conclusions: Vitamin E plus C combination is an effective, safe and inexpensive treatment option in patients with NASH and may be useful to reduce damage from oxidative stress and slow the process leading to cirrhosis.

Keywords: Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitios, Ursodeoxycholic acid, Vitamin E

PE-160

Study of Biochemical and Oxidative Stress Markers in the First-Degree Relatives of Persons with Type 2 Diabetes Stratified by Glucose Tolerance Test

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Aims: The present study has been attempted to compare the relative tolerance to glucose in first-degree relatives of type 2 diabetic patients and estimate the anthropometric, biochemical parameters and markers of oxidative stress in subjects with the different degree of glucose tolerance.

Methods: The study consisted of 34 subjects aged between 20-45 years, with established family history of type 2 diabetes mellitus, who were subjected to oral glucose tolerance test (OGTT). Those without any family history of diabetes served as controls.

Results: Out of the 34 subjects, 5 subjects exhibited high toler-

ance, 18 showed a moderate degree of glucose tolerance and 9 subjects were with low glucose tolerance. Only 2 subjects were categorized as highly intolerant after OGTT. In almost all subjects with glucose tolerance test, the peak plasma glucose level was recorded at 60 minutes after oral glucose administration. In the present study subjects, with a high degree of glucose intolerance showed significantly higher levels of triglyceride (171 ± 9.8**) mg/dl and VLDL levels (34.2 ± 1.9**) mg/dl. A significant increase in the TBARS levels (2.9 ± 0.053**) μg/ml was recorded in subjects with a high degree of glucose intolerance. A corresponding decrease in the reduced glutathione (1.6 ± 2.2) mg/ml and superoxide dismutase activity (0.7 ± 0.08) units/min/mg protein was also recorded.

Conclusions: The study revealed disturbance in the lipid parameters and antioxidant defenses in the first degree relative of diabetic patients even before the establishment of disease.

Keywords: Impaired glucose tolerance, Family history of diabetes, Oxidative stress, Antioxidant enzymes

PE-161

Association with Low Psoas Muscle Area and Non-Alcoholic Fatty Liver Disease in Patients with Inflammatory Bowel Disease

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Aims: Recently, decreased muscle mass has been proposed as an additional risk factor in patients with non-alcoholic fatty liver disease (NAFLD), which have been no studies in patients with inflammatory bowel disease (IBD). We aimed to analyze the clinical associations between low muscle mass and NAFLD, independently other risk factors of NAFLD in IBD patients.

Methods: From January 2004 to December 2017, a total 488 IBD patients with the result of computed tomography (CT) were included, which were classified into two groups according to the presence of NAFLD. The volume of muscle was calculated by area of total psoas muscle in third lumbar region on CT per patient's height^2 (m^2). Low psoas muscle area (LPMA) was defined as the cases in which the volume of muscle less than 545 mm^2/m^2 in men and less than 385 mm^2/m^2 in women.

Results: NAFLD was diagnosed in 49 patients (11.1%) from final 443 IBD patients. Patients in NAFLD group were older (45.1 vs. 38.6 years; P = 0.006), had higher level of body mass index (23.0 ± 2.7 vs. 20.8 ± 3.3 kg/m^2; P < 0.001), more metabolic syndrome (36.7% vs 7.4%; P < 0.001), and had higher proportions of LPMA (51.0% vs. 33.0%; P = 0.019) than those in non-NAFLD group. In the multivariate analysis, metabolic syndrome (Odds ratio [OR]: 8.633), hyperuricemia (OR: 4.662), small bowel resection (OR: 3.453), and the presence of LPMA (OR: 2.994) were significant risk factors of NAFLD in IBD patients. LPMA was an independent risk factor for NAFLD in patients with IBD, which is adjusted by age, gender, traditional metabolic risk factors, disease severity of IBD, and medication.

Conclusions: LPMA is associated with NAFLD in patients with IBD, independent of metabolic risk factors.

Keywords: Non-alcoholic fatty liver disease, Inflammatory bowel disease, Psoas muscle, Computed tomography

PE-162

Nonalcoholic Fatty Liver Disease and Sarcopenia Are Independently Associated with Cardiovascular Risk

Eugene Han[1], Yong-ho Lee[2,3], Young Dae Kim[4], Beom Kyung Kim[2,5,6], Jun Yong Park[2,5,6], Do Young Kim[2,5,6], Sang Hoon Ahn[2,5,6], Byung-Wan Lee[2,3], Eun Seok Kang[2,3], Bong-Soo Cha[2,3], Kwang-Hyub Han[2,5,6], Hyo Suk Nam[4], Ji Hoe Heo[4], and Seung Up Kim[2,5,6]

[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea; [4]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea; [5]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; [6]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: Non-alcoholic fatty liver disease (NAFLD) and sarcopenia have a close association with the increased atherosclerotic cardiovascular disease (ASCVD) risks. This study investigated the interactive influence of NAFLD and sarcopenia on ASCVD risks.

Methods: Data from the Korean National Health and Nutrition Examination Surveys 2008–2011 database were analyzed. The sarcopenia index was calculated using dual-energy x-ray absorptiometry. Sarcopenia was defined as the lowest quintile sarcopenia index value (cutoffs: 0.882 for men and 0.582 for women). NAFLD was defined as comprehensive NAFLD score (CNS) ≥40. Liver fibrosis was assessed using NAFLD fibrosis score (NFS). ASCVD risk was evaluated using ACC/AHA guidelines. ASCVD risk >10% was defined as having a high-risk.

Results: Prevalence of NAFLD and sarcopenia and 31.2% (2,241 of 7,191) and 19.5% (1,400 of 7,191), respectively. The quartile-stratified ASCVD risk scores showed a significant positive association with NAFLD and sarcopenia (all P for trend<0.001). The subjects with both NAFLD and sarcopenia had a higher risk of high-probability in ASCVD risk (odds ratio [OR] = 1.83, P = 0.014), when compared to control subjects without NAFLD and sarcopenia. Among subjects with NAFLD, NFS-defined significant liver fibrosis and sarcopenia additively raised the risk of high-probability in ASCVD risk (OR = 4.15, P < 0.001), when compared to control subject without significant liver fibrosis and sarcopenia.

Conclusions: NAFLD and sarcopenia are significantly associated with the increased risk of ASCVD in general population. In addition, NAFLD with liver fibrosis and sarcopenia are significantly associated with the increased risk of ASCVD in subjects with NAFLD.

Keywords: Nonalcoholic fatty liver disease, Sarcopenia, Cardiovascular, Fatty liver

PE-163

Sarcopenia Is Independently Associated with the Degree of Liver Fibrosis in Patients with Type 2 Diabetes Mellitus

Min Je Sung[1], Tae Seop Lim[1,3], Mi Young Jeon[1,3], Hye Won Lee[1,3], Beom Kyung Kim[1-3], Do Young Kim[1-3], Sang Hoon Ahn[1-3], Kwang-Hyub Han[1-3], Jun Yong Park[1-3], and Seung Up Kim[1-3]

[1]Department of Internal Medicine, [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: Sarcopenia is significantly associated with degree of liver fibrosis in patients with chronic liver diseases including non-alcoholic fatty liver disease and chronic hepatitis B. We investigated the association between sarcopenia and fibrotic burden in liver in patients with type 2 diabetes mellitus (T2DM).

Methods: Patients with T2DM who received comprehensive medical health check-up between 2010 and 2018 were recruited. Muscle mass was assessed by computed tomography (CT) analysis at the 3rd lumbar vertebra. Fibrotic burden was assessed using fibrosis-4 index (FIB-4). The study population was divided according to quartile stratification of lumbar skeletal muscle index (LSMI) (Q1 to Q4) and patients with lowest quartile (Q1) were considered as having sarcopenia.

Results: In total, 309 patients with T2DM were recruited. Of these, 75 (24.3%) had sarcopenia. Sarcopenic patients were significantly older and had higher FIB-4 and prothrombin time, whereas they had significantly lower alanine aminotransferase, lower body mass index (BMI), and lower LSMI than those of non-sarcopenic patients (all $P < 0.05$). LSMI and FIB-4 by quartile stratification were significantly correlated ($P = 0.003$). BMI and FIB-4 were significantly associated with sarcopenia in univariate analysis (all $P < 0.05$) and subsequent multivariate analysis found that higher BMI was independently associated with the reduced risk of sarcopenia (odds ratio [OR] = 0.738, 95% confidence interval [CI], 0.654-0.833, $P < 0.001$), whereas higher FIB-4 was independently associated with the increased risk of sarcopenia (OR = 1.778, 95% CI, 1.154-2.716, $P = 0.008$). Among the patients with BMI< 25 kg/m^2 (n = 165), sarcopenic patients (n = 54, 32.7%) had significantly higher FIB-4 than that of non-sarcopenic patients (n = 111, 67.3%) (1.66 vs. 1.38, $P = 0.004$).

Conclusions: Sarcopenia is independently associated with fibrotic burden in patients with T2DM, regardless of BMI. Further studies are required to determine whether interventions to improve muscle mass in this population with T2DM can regress fibrotic burden in liver.

Keywords: Sarcopenia, Liver fibrosis, Chrnoic liver disease, Muscle mass

PE-164

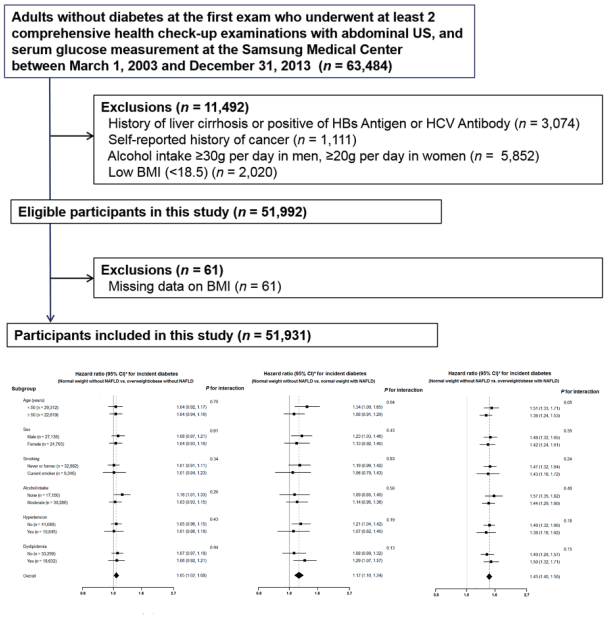
Lean Nonalcoholic Fatty Liver Disease and Development of Diabetes Mellitus: A Cohort Study

Dong Hyun Sinn[1], Joo Hyun Oh[1], Danbee Kang[2], Soo Jin Cho[3], Seung Woon Paik[1], Eliseo Guallar[4,5], Juhee Cho[2,4,5], Geum-Youn Gwak[1]

[1]Department of Medicine, [2]Department of Clinical Research Design and Evaluation, SAIHST, [3]Center for Health Promotion, [4]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University, [5]Departments of Epidemiology and Medicine and Welch Center for Prevention, Jonhs Hopkins Medical Institutions, Baltimore, USA

Aims: Body mass index (BMI) is an indicator of metabolic health, but nonalcoholic fatty liver disease (NAFLD), a condition associated with metabolic derangement, is observed in lean individuals. To date, metabolic consequence of lean NAFLD has not been well characterized.

Methods: A total of 51,931 adult men and women without diabetes mellitus (DM), history of liver disease or cancer at baseline who participated in a regular health screening exam between March 2003 and December 2013 were analyzed for incident DM during follow-up. The risk of incident DM for lean participants with NAFLD, overweight/obese participants without NAFLD and overweight/obese participants with NAFLD was compared to lean participants without NAFLD. Fatty liver was diagnosed by ultrasonography, and NAFLD severity was assessed by the NAFLD fibrosis score (NFS).



Results: During 236,446.6 person-years of follow-up (median follow-up of 4.0 years), 5,370 participants developed DM. In fully-adjusted model, the hazard ratios (HRs) were 1.18 (95% CI = 1.03, 1.35), 1.06 (95% CI = 0.98, 1.14), and 1.45 (95% CI = 1.34, 1.57) for lean participants with NAFLD, overweight/obese partic-

ipants without NAFLD, overweight/obese participants with NAFLD compared to lean participants without NAFLD, respectively. Compared to lean participants without NAFLD, the fully-adjusted HR for incident DM were 1.31 (1.13, 1.52) and 2.74 (2.11, 3.56) for lean NAFLD participants with low NFS (<-1.455) and with intermediate to high NFS (≥-1.455) respectively.

Conclusions: In this large cohort study, lean participants with NAFLD had an increased risk of DM. In addition, this association was stronger in participants with evidence of more advanced NAFLD as indicated by the NFS. Lean NAFLD individuals may need to be carefully monitored and managed early to prevent DM.

Keywords: Body mass index, Diabetes mellitus, Nonalcoholic fatty liver disease, Fibrosis

PE-165

Routinely Available Noninvasive Tests Discriminate Advanced Fibrosis Due to NASH in the Phase 3 STELLAR Trials of the ASK1 Inhibitor Selonsertib

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Aims: Liver biopsy is currently the reference standard for fibrosis staging, but is an invasive procedure with limitations. There is a major unmet need for accurate, readily available noninvasive tests (NITs) to identify patients with advanced fibrosis due to NASH. Our aim is to describe the performance of NITs using the baseline data from the Phase 3 STELLAR studies of the ASK1 inhibitor selonsertib (SEL).

Methods: The STELLAR studies (NCT03053050 and NCT03053063) enrolled patients with bridging fibrosis (F3) or compensated cirrhosis (F4) due to NASH (NAFLD Activity Score [NAS] ≥3). Baseline liver biopsies were centrally read according to the NASH CRN fibrosis classification and noninvasive markers of fibrosis, including the NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) test, and liver stiffness (LS) by transient elastography (TE; FibroScan®) were measured. The performance of these tests to discriminate advanced (F3-F4) fibrosis was evaluated using AUROCs with 5-fold cross-validation repeated 100x. Optimal thresholds for F3-F4 fibrosis were selected based on the literature. Data presented are from an interim analysis on 1 May 2018.

Results: A total of 4467 patients (median age 58 years, 55% women, 72% Caucasian, 59% with diabetes) were screened. In the 3220 with evaluable histology, median biopsy length was 2.0 cm, 8% F0, 9% F1, 13% F2, 31% F3, 40% F4, 59% with NAS ≥5. Median values of NFS, FIB-4, ELF, and LS by TE increased with worsening fibrosis (-0.962/1.19/9.21/8.8 kPa in F0-F2 vs 0.342/2.20/10.39/16.5 kPa in F3-F4 respectively). AUROCs ranged from 0.75 to 0.80 to discriminate advanced fibrosis (Table). When tests were combined, performance characteristics improved and PPVs ≥98% were possible.

Table: Diagnostic Performance of NITs to Discriminate Advanced Fibrosis (F3-F4)

Test	Prevalence of F3-F4	AUROC (95% CI)	Cut-off	Sensitivity	Specificity	PPV	NPV
NFS n=2309	78%	0.75 (0.75, 0.75)	≥ -1.455	90%	37%	83%	52%
			≥ 0.676	39%	89%	93%	30%
FIB-4 n=3125	71%	0.78 (0.78, 0.78)	≥ 1.3	82%	57%	83%	56%
			≥ 2.67	36%	93%	93%	37%
ELF n=3183	71%	0.80 (0.80, 0.80)	≥ 9.8	74%	73%	87%	53%
			≥ 11.3	20%	98%	95%	33%
LS by TE n=1760	84%	0.80 (0.79, 0.8)	≥ 9.9 kPa	83%	61%	92%	41%
			≥ 11.4 kPa	75%	71%	93%	36%

Conclusions: In these large, global phase 3 trials of SEL, routinely available NITs demonstrated acceptable diagnostic performance for the discrimination of advanced fibrosis due to NASH.

Keywords: NASH, Selonsertib, Gilead, Noninvasive test, STELLAR, ASK1 inhibitor, MAFLD

PE-166

Clinical Utility and Application of Noninvasive Tests in Selecting Patients with Advanced Fibrosis Due to NASH in the Phase 2 ATLAS Trial

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Aims: Liver biopsy is a barrier to clinical trial enrollment in NASH. We describe the utility of noninvasive tests (NITs) to en-

roll patients with advanced fibrosis (F3-F4) due to NASH.

Methods: The ATLAS study (NCT03449446) enrolled patients based on: 1) a biopsy showing F3-F4 fibrosis per the NASH CRN classification (the biopsy cohort); or 2) in the absence of a prior biopsy, an ELF test ≥9.8 and liver stiffness (LS) by transient elastography (TE; FibroScan) ≥14.0 kPa using the XL probe (the NIT cohort). Patients in the NIT cohort had baseline biopsies and were randomized regardless of results. Analyses are based on an interim data cut.

Results: Of the 645 screened patients with evaluable fibrosis stage (median age 59 years, 62% women, 61% with diabetes, median BMI 33.7 kg/m^2), 395 were enrolled. Fifty-five (14%) qualified based on NIT criteria; F3-F4 fibrosis was confirmed in 87% (48/55) (4% F0, 4% F1, 5% F2, 22% F3, 65% F4). Patients in the biopsy cohort with F3-F4 fibrosis had demographics, liver biochemistry, and serum fibrosis markers similar to those in the NIT cohort, but with higher LS by TE (Table). The proportions of patients with NAS ≥4 (87% vs 86%) and cirrhosis (65% vs 53%; P = 0.09) did not differ between the NIT and biopsy cohorts. Within the NIT cohort, biopsy length was shorter in patients with F0-F2 vs F3-F4 (1.3 vs 2.2 cm; P = 0.18). Patients with F0-F2 fibrosis also had lower BMI (31.0 vs 34.4 kg/m^2; P = 0.11), less diabetes (43% vs 75%), and less lobular inflammation and ballooning.

Table: Baseline Laboratory and Histological Features

Parameter	Screen Failures F0-F2 (n=148)	Biopsy Cohort F3-F4 (n=442)	NIT Cohort*	
			F0-F2 (n=7)	F3-F4 (n=48)
ALT, U/L	32	42	21	47
FIB-4	1.2	2.0	0.9	2.3
ELF	8.9	10.0	10.1	10.6
LS by TE†, kPa	9.0	14.8	14.4	21.2
Lobular inflammation grade 3	22 (15)	257 (58)	1 (14)	29 (60)
Ballooning grade 2	50 (34)	348 (79)	4 (57)	39 (81)

Data are median or n (%).
* Patients in the NIT cohort are not included in the screen failures or biopsy cohort.
† LS using FibroScan XL probe. Data in n=123 screen failures, n=363 with F3-F4 in the biopsy cohort, and all in the NIT cohort.

Conclusions: In this Phase 2 trial of patients with NASH, a combination of ELF and LS by TE identified the target population in 87% of patients. Enrollment based on NITs should be considered for future NASH studies to reduce reliance on biopsy.

Keywords: NASH, NAFLD, Noninvasive test, ATLAS trial, Fibrosis

PE-167

Atrial Fibrillation Is Associated with Advanced Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease

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Aims: Although non-alcoholic fatty liver disease (NAFLD) has been reported to be independently associated with increased incidence of atrial fibrillation (AF), the association of advanced liver fibrosis with AF in NAFLD patients has not been established. Advanced liver fibrosis in patients with NAFLD is related to all-cause, cardiovascular, and liver-related mortality. We aimed to investigate association between atrial fibrillation and advanced liver fibrosis in patients with NAFLD.

Methods: From January 2010 to December 2017, 6293 NAFLD patients aged 35 years and older were enrolled. All electrocardiograms were diagnosed after a review by a skilled cardiologist. The stage of liver fibrosis is assessed by new adjusted, non-invasive scoring model including NAFLD fibrosis score (NFS) and Fibrosis-4 (FIB-4) index, which was determined as the both low and high cut-off value (COV).

Results: Of 6293 patients with NAFLD, 59 (0.9%) were diagnosed with AF. The AF patients were older (52.0 vs. 64.6 years, P = 0.001), had higher BMI (25.2 vs. 26.6 kg/m^2, P = 0.001) and waist circumference (84.0 vs. 89.9 cm, P = 0.001) compared to non-AF patients. AF was an independent risk factor for advanced fibrosis, assessed by both COVs of NFS (adjusted for obesity, hypertension, high sensitivity C reactive protein, lipid profile, and sex, ORs = 2.48 to 3.38, P < 0.01 in the low-COV group, ORs = 10.79 to 14.55, P < 0.01 in the high-COV group, respectively. In addition, AF was an independent risk factor for advanced fibrosis, assessed by both COVs of FIB-4 (adjusted for obesity, hypertension, high sensitivity C reactive protein, lipid profile, and sex, ORs = 2.54 to 2.86, P < 0.01 in the low-COV group, ORs =3.64 to 5.97, P < 0.05 in the high-COV group, respectively).

Conclusions: AF may be an independent risk factor for advanced liver fibrosis in patients with NAFLD.

Keywords: Atrial fibrillation, Advanced liver fibrosis, Non-alcoholic fatty liver disease

PE-168

Prevalence of Pre-Diabetes, Diabetes, Abdominal Obesity and Hypertension among the Service Communities of Bhilai City of India

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Aims: The main objective of this study was to estimate the prevalence of diabetes, pre-diabetes and obesity among service community of Bhilai city.

Methods: The subjects for the study were randomly selected and were belonging to service community. The study was carried out on about 500 subjects who voluntarily participated in the study. The prevalence of pre-diabetes, diabetes, and hypertension were determined by American diabetes association criteria and central obesity was measured by body mass index (BMI) which was calculated from height and weight of the subjects employing the standard formula.

Results: The present study revealed that the incidence of diabetes among the employees of police community is about 10%. The incidence is significantly high among females as compared

to males. The average age group of diabetic subjects is around 50 yrs. About 30 - 35% of diabetics have hypertension as well as BMI. The waist circumference which is an indicator of central obesity is high in about 30% of diabetic subjects. The prevalence of pre-diabetes is significantly high (30%) as compared to diabetes and is prevalent in the age group of 30 40 yrs. About 70% of pre-diabetics have high BMI, whereas the percentage of subjects with increased waist circumference is lower than that of diabetic group. Only about 10% of pre-diabetics showed high blood pressure. A significant percentage of normal subjects did exhibit high BMI.

Conclusions: The alarming increases in obesity component resulting in metabolic syndrome, seems to be behind the twin epidemic of type 2 diabetes and cardiovascular disease currently sweeping the Indian subcontinent. Sedentary life style and increased popularity and easy-availability of energy-dense food are the driving force for this growing menace. The study revealed a high incidence of prediabetes and diabetes among members of professional communities in Bhilai city.

Keywords: Diabetes, Service community, Prediabetes, Hypertension

PE-169

Nonalcoholic Steatohepatitis Is Associated with a Higher Risk of Advanced Colorectal Neoplasm

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Aims: Nonalcoholic fatty liver disease (NAFLD) is known to increase the risk of adenomatous colonic polyps. However, the role of screening colonoscopy in patients with biopsy-proven NAFLD in detecting advanced colorectal neoplasm is not clearly evidence-based. Therefore, we investigated whether the histological severity of NAFLD is associated with advanced colorectal neoplasm.

Methods: This study included patients ≥40 years old who underwent routine colonoscopy between 2013 and 2018 within a biopsy- evaluated prospective NAFLD cohort. Advanced colorectal neoplasm was defined as an adenomatous polyp greater than 10 mm in diameter and/or with villous histology and/or with high-grade dysplasia or adenocarcinoma.

Results: Among the 472 patients with biopsy-proven NAFLD who underwent colonoscopy, the prevalence of advanced colorectal neoplasm was 10.2% (n = 48). Patients with advanced colorectal neoplasm had a higher stage of hepatic fibrosis than those with a low-grade adenomatous polyp (P = .005). Multivariable logistic regression analysis revealed that the presence of histologically confirmed hepatic steatosis was an independent risk factor for adenomatous colorectal polyp (odds ratio [OR], 3.89; 95% confidential interval [CI], 1.41–10.7; P = .009) and the presence of nonalcoholic steatohepatitis (NASH) was an independent risk factor for advanced colorectal neoplasm (OR, 9.33; 95% CI, 1.14–76.3; P = .037).

Conclusions: The presence of biopsy-proven NASH was significantly associated with an increased risk of advanced colorectal neoplasm among patients with NAFLD. This finding may alert physicians to conduct screening colonoscopy in patients with NASH to detect advanced colorectal neoplasm early.

Keywords: Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Advanced colorectal neoplasm, Fibrosis, Hepatocellular ballooning

PE-170

Weight Loss Significantly Reduces the Risk of Chronic Kidney Disease Development

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Aims: Weight loss is regarded as a pivotal treatment strategy in non-alcoholic fatty liver disease (NAFLD). However, there is a lack of data evaluating whether weight loss affects long-term kidney function in this population.Therefore, we investigated the impact of weight changes on adverse kidney outcomes in NAFLD patients using a community-based, prospective cohort with a 12-year follow-up.

Methods: Among 10,030 participants from the Korean Genome Epidemiology Study, 1,774 NAFLD patients were included in this study. Patients were categorized into four groups according to the quartiles of time-averaged percent weight change (TA-%weight change). Study outcomes were development of chronic kidney disease (CKD) and rapid decline of kidney function.

Results: The median value of TA-%weight change was –1.3% (interquartile range, –4.2 to 1.1). During a mean follow-up of 108.7 ± 44.5 months, CKD developed in 510 patients (28.7%). Patients in the first quartile (TA-%weight change < –4.2%) had a significantly lower risk of CKD development (hazard ratio [HR] = 0.531, 95% confidence interval [CI] = 0.409-0.690) and rapid decline of kidney function (HR = 0.598, 95% CI = 0.458-0.782), compared with patients with minimal changes. Decreased risk of CKD development in patients of the first quartile remained significant in the overweight (HR=0.528, 95% CI = 0.372-0.751) and obese (HR = 0.482, 95% CI = 0.307-0.755) groups.

Conclusions: In conclusion, this study is the first to demonstrate that weight loss, above an average of 4.2%, was associated with significant risk reduction of CKD development and rapid

decline in kidney function. It suggests that significant and sustained weight loss may improve long-term kidney outcomes in patients with NAFLD.

Keywords: Chronic kidney disease, Non-alcoholic fatty liver disease, Weight reduction, Non-alcoholic steatohepatitis

PE-171

The Invasive and Noninvasive Assessments for Liver Fibrosis in Korean Nonalcoholic Fatty Liver Disease Patients

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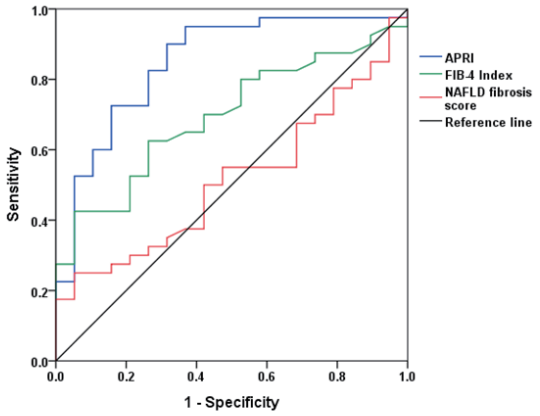
Aims: The only way to definitively confirm of nonalcoholic steatohepatitis (NASH) is a liver biopsy. However, due to its invasive nature, the noninvasive tests have been developed. The prevalence of nonalcoholic fatty liver disease (NAFLD) is a median of 20% in the Korean population and NAFLD has become an important public health issue in Korea. However, there were few studies related to diagnosis of NASH on Korean NAFLD patients in previous studies.

Methods: We prospectively analyzed a total of 59 patients (mean age: 48 ± 14 years, female: 28) with NAFLD who performed liver biopsy at Dong-A university hospital from November, 2017 to January, 2019. Clinical characteristics, the results of liver biopsy and noninvasive testing, such as AST to platelet ratio index (APRI), fibrosis-4 (FIB-4) index and NAFLD fibrosis score were recorded. We divided patients into 2 groups (steatosis group and steatohepatitis group). Metabolic parameters of 2 groups were analyzed.

Results: The number of steatohepatitis diagnosed by liver biopsy is 40 (68%) and the number of liver fibrosis patients diagnosed by APRI, FIB-4 index and NAFLD fibrosis score is 29 (49%), 20 (34%) and 32 (54%), respectively. The AUROC curves of APRI, FIB-4 index and NAFLD score were 0.849 (95% Confidence interval [CI] : 0.740-0.957), 0.695 (95% CI : 0.545-0.762) and 0.515 (95% CI : 0.365-0.665), respectively. Steatohepatitis group (16 patients) showed high insulin resistance (70% *vs*. 38% $P = 0.024$), metabolic syndrome (75% *vs*. 38%, $P = 0.008$), central obesity (93% *vs*. 25%, $P < 0.001$) and fasting glucose level (65% *vs*. 31%, $P = 0.022$), compared to steatosis group (40 patients).

Conclusions: We cautiously consider to do liver biopsy or noninvasive assessment for liver fibrosis in NAFLD patients with metabolic syndrome, obesity or diabetes mellitus, even if nonalcoholic fatty liver diagnosed by ultrasound.

Figure 1. Receiver operator characteristic curve (ROC) of the noninvasive testing for nonalcoholic fatty liver disease



Noninvasive testing	*P* value	Area under the curve (AUC)	95% confidence interval	
			Lower limit	Upper limit
APRI	< 0.001	0.849	0.740	0.957
FIB-4 index	0.016	0.695	0.545	0.762
NAFLD fibrosis score	0.852	0.515	0.365	0.665

APRI, aspartate aminotransferase to platelet ratio index; FIB-4 index, Fibrosis-4 index; NAFLD fibrosis score, nonalcoholic fatty liver disease fibrosis score

Keywords: Steatohepatitis, NAFLD, Liver fibrosis, Liver biopsy

PE-172

The Grade of Nonalcoholic Fatty Liver Disease Is an Independent Risk Factor for Gallstone Disease

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Aims: There are some reports about association between nonalcoholic fatty liver disease (NAFLD) and gallstone disease (GD) because of sharing risk factors. However, there is no report about an association between grades of NAFLD and GD. Therefore, the aim of this study was to know whether grade of NAFLD could be an independent risk factor affecting GD in a Korean population.

Methods: This study enrolled a total of 7,886 subjects who completed a questionnaire and underwent ultrasound and medical checkup at the Health Promotion Center of Jeju National University Hospital in Korea from January 2009 to December 2017. Grade of fatty liver and presence of gallstones were investigated by abdominal ultrasound. The body Mass index, biochemical parameters were checked, and age, metabolic syndrome and sex were collected based on their medical records. Univariate and multivariate analyses were performed to identify risk factors affecting GD.

Results: The estimated prevalence of NAFLD and GD were 40.5% and 4.5% respectively. In the univariate analysis, risk factors affecting GD were the age, NAFLD, metabolic syndrome, fasting blood glucose, high density lipoprotein (HDL)-cholester-

ol, aspartate aminotransferase, alanine aminotransferase. In the multivariate logistic regression analysis, independent risk factors were older age and higher grade of NAFLD.
Conclusions: Older age and higher grade of NAFLD are independent risk factors affecting GD. There is a strong correlation between grade of NAFLD on abdominal ultrasonography and GD.

PE-173

Appropriateness of Liver Biopsy for Nonalcoholic Fatty Liver Disease during Laparoscopic Cholecystectomy for Gallstone Disease

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Aims: Obesity is well known as a risk factor for gallstone disease and is also a risk factor for fatty liver. Although, liver biopsy is particularly useful in patients without definite clinical manifestations, liver biopsy is invasive and is not recommended except in special case. However, hepatic biopsy is not a relatively risky procedure during laparoscopic cholecystectomy. Therefore, we investigated the clinical characteristics in biopsy proven non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in gallstone disease patients during laparoscopic cholecystectomy for gallstone disease.
Methods: We retrospectively reviewed 288 medical records with gallstone disease who underwent laparoscopic cholecystectomy with liver biopsy from 2006 to 2017. Univariate and multivariate logistic regression were performed to evaluate the association between clinical factors and fatty liver.
Results: Ninety-six (33.3%) patients were diagnosed as fatty liver. Mean BMI of the patients was 24.5 kg/m^2. (24.1-25.0) In univariate analysis, 6 clinical factors involved the fatty liver: BMI, Hb, ALP, AST, DM, and Liver disease. However, 4 clinical factors were involved in the multivariate logistic regression model. (BMI: OR = 1.210 (1.111-1.318), $P < 0.001$; ALP: OR = 0.991 (0.984-0.998), $P = 0.018$; DM: OR = 2.618 (1.135-6.204), $P = 0.024$; and Liver disease: OR = 2.193 (1.667-3.049), $P < 0.001$).
Conclusions: The liver biopsy could be recommended in high BMI patients with DM or Liver diseases.

PE-174

Risk Factors for Incident Nonalcoholic Fatty Liver Disease and Liver Fibrosis in Breast Cancer Survivors

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Aims: Data on nonalcoholic fatty liver disease (NAFLD) in patients with breast cancer are scarce. We aimed to investigate clinical features and risk factors of NAFLD in breast cancer survivors.
Methods: In this prospective, single-center cohort study, we started screening breast cancer patients from August 2018, who had been followed after appropriate anticancer treatments including surgery, radiotherapy, and chemotherapy in the Cancer Center for Women in our institution. Patients in remission (defined as 'breast cancer survivors') with fatty liver on ultrasound at baseline or during follow-up evaluations were referred to the Liver Center in the same institution. Exclusion criteria were i) significant alcohol consumption; ii) other causes of liver diseases, such as viral or autoimmune; iii) evidence of recurrent breast cancer or serious comorbidities (other malignancies, cardiopulmonary diseases, etc.). As of March 2019, a total of 231 patients who gave informed consents were enrolled, and a cross-sectional analysis was conducted.
Results: Mean age was 53.3±8.2 years. Body mass index (BMI) was 25.2±3.4 kg/m^2, and waist circumference was 89.3±8.7 cm. Median time period from first visit to consultation was 30.4 months (interquartile range [IQR], 16.6-51.5). For hormonal therapy, 147 patients were taking tamoxifen (63.6%) for 36.5 months (median; IQR, 18.4-54.1) and 50 were on letrozole (21.6%) for 20.0 months (median; IQR, 13.3-51.8), respectively. Metabolic syndrome (MetS) was found in 83 patients (35.9%). Homeostasis model assessment-insulin resistance (HOMA-IR) was 2.14 (median; IQR, 1.52-2.96). Serum AST/ALT were 25.0 IU/L (IQR, 21-31)/23.0 IU/L (IQR, 16-33), respectively. Liver stiffness (LS) by transient elastography was 4.2 kPa (median; 2.4-14.6). Controlled attenuation parameter (CAP) was 281.5 dB/m (median; IQR, 243-320). At baseline, 103 patients had NAFLD at baseline (44.6%), and 128 patients developed NAFLD during follow-up ('incident NAFLD', 55.4%). Patients with incident NAFLD were more commonly on tamoxifen (72.4% vs. 17.3%, $P = 0.011$), had lower baseline BMI (24.5 vs. 26.1 kg/m^2, $P < 0.001$), and were less commonly associated with MetS (28.1% vs. 45.6%, $P = 0.006$) compared to those with baseline NAFLD. Patients with baseline NAFLD had lower appendicular skeletal muscle mass (ASM)-to-BMI ratio (0.61 vs. 0.65, $P = 0.001$) as well as ASM% (24.9% vs. 26.0%, $P = 0.003$). LS was not significantly different between patients with baseline NAFLD vs. those with incident NAFLD (4.8 kPa vs. 4.4 kPa, $P = 0.057$). In multiple linear regression analyses, risk factors for higher LS were i) HOMA-IR ($P < 0.001$), ASM-BMI ($P = 0.034$), percentage fat ($P = 0.020$) in overall patients; ii) HOMA-IR ($P < 0.001$), ASM-BMI ($P = 0.018$), percentage fat ($P = 0.028$) *in patients with BMI≥25; iii) HOMA-IR* ($P < 0.001$) in patients with BMI<25.
Conclusions: Incident NAFLD in breast cancer survivors was associated with lower BMI and tamoxifen use, whereas preexisting NAFLD was associated with lower muscle mass and MetS. HO-

MA-IR was an independent predictor of liver fibrosis regardless of BMI.

Keywords: Breast cancer, Fatty liver, Hepatic fibrosis, Risk factor

PE-175

Features of the Prevalence of Risk Factors for Non-Alcoholic Fatty Liver Disease among Residents of the City of Bishkek (Kyrgyzstan)

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Aims: Assess the prevalence of NAFLD risk factors among residents of the city of Bishkek (Kyrgyzstan).

Methods: In the course of screening, 2389 people who applied for various reasons to family medicine centers in Bishkek, according to the exclusion criteria, 1005 people took part in the study, including 678 (68%) women and 327 (32%) men aged 17 to 96 years old. To achieve this goal, with the informed consent of the patients, the following parameters were measured: waist circumference, biochemical blood test (AST, ALT), data from the anamnesis (smoking, diabetes mellitus) and liver ultrasound.

Results: The data presented in the table.

Sign	Men (n = 327)	Women (n = 678)	Significance
Young age (25-44л) (n = 168)	78 (24%)	90 (13%)	p<0,01
Midl age (45-59л) (n = 573)	165 (50%)	408 (60%)	p<0,01
Elderly age (65-74л) (n = 201)	69 (21%)	132 (20%)	p<0,01
Old age (75-90л) (n = 63)	15 (4%)	48 (7%)	p<0,01
Waist (м ›102см; w ›88см) (n = 50)	102 (22%)	348 (77%)	p<0,01
ALT (›38 ЕД/л)	237 (23%)	455 (45%)	p<0,01
AST (›41 ЕД/л)	114 (11%)	183 (18%)	p<0,01
Smoking	204 (20%)	87 (9%)	p<0,01
Diabetes	180 (18%)	387 (39%)	p<0,01

Conclusions: Middle-aged women prevailed among the patients (40%). In individuals with NAFLD, the leading risk factor was abdominal obesity (44.5%), with a high level of AST (29%) and a high level of ALT (68%).

Keywords: NAFLD, Metabolic syndrome, Waist circumference, Biochemical blood test

PE-176

Serum Biomarkers to Differentiate Non-Alcoholic Steatohepatitis, Advanced Fibrosis, and Severe Steatosis from Mild Form of Non-Alcoholic Fatty Liver Disease

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Aims: With increasing prevalence worldwide, diagnosis and determining of severity for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) is becoming more important. In this study, we evaluated a diverse set of biomarkers to differentiate NASH, advanced fibrosis, and severe steatosis from mild form of NAFLD.

Methods: This is a single-center prospective cross-sectional study of patient with biopsy-confirmed NAFLD. The patients were undertaken laboratory test, liver biopsy, and eighteen kind of serum biomarkers. Sera were stored at -80℃ and measured using the Luminex Multiplex platform. We tried to find specific biomarkers associated with NASH, advanced fibrosis, and severe steatosis using linear regression model.

Results: A total of 88 patients were enrolled. Among 88 participants (42% male, median age 52.5 years), 51.1% had NASH, 19.3% had advanced fibrosis (stage 3-4), and 20.5% had severe steatosis(stage 3). There was no statistically significant biomarker associated with NASH. In advanced fibrosis, however, sCD40L was statistically significant predictor (OR = 0.927; 95% CI 0.869-0.990, P = 0.023). In severe steatosis, sCD40L (OR = 1.075; 95% CI 1.014-1.140, P = 0.015), PAI-1 (OR = 1.019; 95% CI 1.014-1.140, P = 0.007), and aPAI-1 (OR = 1.035; 95% CI 1.008-1.063, P = 0.011) showed significant results.

Conclusions: We failed to find out specific biomarkers to differentiate NASH. However, sCD40L showed significant relevance about advanced fibrosis. sCD40L, PAI-1, and aPAI-1 showed significance about severe steatosis. Further investigations should be conducted to find out novel biomarkers to replace liver biopsy.

Keywords: Biomarker, NAFLD

PE-177

The High Occurrence of Non-Alcoholic Steatohepatitis with Fibrosis in Patients with Moderate Fatty Liver Accompanied by Metabolic Syndrome

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Aims: The prevalence of steatohepatitis, which can progress to cirrhosis and hepatocellular carcinoma, among patients with non-alcoholic fatty liver disease (NAFLD) has been known to be about 20%. We evaluated the occurrence of steatohepatitis and fibrosis in liver biopsy specimens of patients with NAFLD accompanied by metabolic syndrome.

Methods: We retrospectively analyzed nine NAFLD patients who underwent percutaneous liver biopsy at the fatty liver clinic of Seoul Paik Hospital from August 2018 to February 2019. They were recommended to reduce body weight with diet program and exercise to treat NAFLD at our fatty liver clinic. All of them were diagnosed with fatty liver equal to or more than mild to

moderate grade by ultrasonography. Also, all of them had at least one of the metabolic syndrome conditions such as hypertension, diabetes mellitus (DM), and hyperlipidemia. A total of 9 HCC patients (M:F=2:7; Age: 50.6 ± 13.4 years; BMI: 30.2 ± 5.9 kg/m^2 ;serum ALT level 45(27-222 IU/L); Grade of fatty liver, mild to moderate: moderate: moderate to severe = 4:1:4) were subjected. One had hypertension only, one DM only, two both of hypertension and DM, four hyperlipidemia, and the last one had all of them.

Results: All nine patients had steatohepatitis in liver biopsy specimens. Seven patients had moderate grade and two showed severe lobular inflammation. Eight of nine showed the development of fibrosis in the liver. Two had 1/4 stage fibrosis, two of 2/4, and four of 3/4. Transient elastography (TE) was performed in 7 patients, of which TE level was lower than expected in patients with fibrosis of more than stage 3. There was no relationship between the severity of fibrosis and the level of TE. There was no difference in the severity of inflammation grade and fibrosis stage according to the grade of fatty liver, the existence of fatty pancreas and atherosclerosis, the percentage of body fat, and BMI.

Conclusions: The patients with equal to or more than mild to moderate fatty liver accompanied by metabolic syndrome have a very high chance to develop steatohepatitis and fibrosis. Therefore, more strict body weight reduction by diet program is needed in these patients.

Keywords: Non-alcoholic fatty liver disease, Fatty liver, Fibrosis, Metabolic syndrome

PE-178

The Value of Controlled Attenuation Parameter in Fibrosis Prediction by Liver Stiffness in Nonalcoholic Steatohepatitis

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Aims: Liver stiffness measurement (LSM) tends to overestimate fibrosis stage in nonalcoholic fatty liver disease (NAFLD). Controlled attenuation parameter (CAP), provided by LSM device, has been introduced for noninvasive quantification of hepatic steatosis. This study aimed to determine the role of CAP values in predicting liver fibrosis stages by LSM in nonalcoholic steatohepatitis (NASH).

Methods: One hundred eighty-four patients with biopsy proven NASH had LSM and CAP evaluated at baseline. Among them, 130 patients had 1-year follow up LSM and analyzed for the changes of LSM after pioglitazone or ursodeoxycholic acid (UDCA) treatment.

Results: When CAP values were grouped by tertiles, lower tertile ranged 223-310, middle 311-339, and higher 340-400 dB/m. In Kleiner fibrosis stage F0-1, LSM values increased at higher CAP tertile (P = 0.001), and in F2, at middle and higher tertiles (P = 0.027). No differences across CAP tertiles were noticed in F3-4 (P = 0.752). Receiver operating characteristic curves for LSM cutoff in diagnosis of F≥2 identified 8.05 kPa for lower CAP tertile, 9.35 kPa for middle, and 10.55 kPa for higher tertile. When changes in proportion of high LSM (F≥2) were assessed among pioglitazone and UDCA treated patients using different LSM cutoffs by CAP tertiles, pioglitazone treated patients demonstrated decrease in proportion of high LSM when UDCA group failed to show significant changes.

Conclusions: LSM in NASH may overestimate stages of liver fibrosis especially in patients with high CAP values. Interpretation of LSM in association with simultaneously measured CAP scores may provide more helpful information sparing unnecessary liver biopsy.

Keywords: Fibroscan, Controlled attenuation parameter, Nonalcoholic steatohepatitis, Liver fibrosis

PE-179

Predictors of Sarcopenia in Obese Korean Population

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Aims: Sarcopenia is not only associated with obesity, but also with cardiometabolic diseases and liver fibrosis. We investigated the prevalence of sarcopenia and its predictors in obese subjects.

Methods: Living-related liver donors and subjects who received a comprehensive medical health check-up were recruited. Obesity was defined as body mass index (BMI) ≥ 25 kg/m^2. Muscle mass was assessed using computed tomography (CT) at the 3rd lumbar vertebra. Cardiometabolic disease risk was assessed using Atherosclerotic Cardiovascular Disease 10-year risk (ASCVD) and fibrotic burden was assessed using the fibrosis-4 index (FIB-4). The study population was divided by quartile stratification of the lumbar skeletal muscle index (LSMI) (Q1 to Q4) and patients with lowest quartile (Q1) were considered as having sarcopenia.

Results: Among 466 obese subjects (86 donors and 380 subjects with health check-up), 53 (11.4%) had sarcopenia. Subjects with sarcopenia were significantly older (mean 53.3 vs. 66.6 years) and had higher ASCVD score (mean 14.95 vs. 23.29), FIB-4 (mean 1.57 vs. 1.16), prevalence of hypertension (62.3 vs. 46.0%) and diabetes (45.3 vs. 31.0%), whereas they had significantly lower BMI (mean 26.4 vs. 27.4 kg/m^2), estimated glomerular filtration rate (mean 81.7 vs. 93.4 ml/min/1.73m2), and LSMI (mean 43 vs. 56 cm^2/m^2) than those of subjects without sarcopenia (all P < 0.05). Multivariate analysis found that higher BMI (odd ratio [OR] = 0.592, 95% confidence interval [CI] 0.440-0.797, P = 001) was independently associated with a reduced risk of sarcopenia, whereas higher ASCVD score (OR =

1.042, 95% CI 1.018-1.066, *P* = 0.001) and FIB-4 (OR = 1.715, 95% CI 1.053-2.794, *P* = 0.030) were independently associated with an increased risk of sarcopenia.

Conclusions: Sarcopenia is significantly associated with lower BMI, higher fibrotic burden, and higher cardiovascular risk in obese Korean population.

Keywords: Sarcopenia, Obesity, Liver disease, Metabolic disease, Body mass index

PE-180

Putative Relationship between Changes in Body Composition and Metabolic Characteristics under Lifestyle Intervention in Patients with Nonalcoholic Fatty Liver Disease

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Aims: Weight loss through lifestyle intervention(LSI) is the mainstay of treatment for patients withnonalcoholic fatty liver disease(NAFLD). The aim was to investigate putative effects of LSI on the changes in parameters of body composition and metabolic characteristics.

Methods: Patients who were diagnosed with NAFLDwere prospectively enrolledsince July 2016in this single-center prospective cohort study. Diagnosis of NAFLD was based on the presence of fatty change in the liver on ultrasound as well as the absence of significant alcohol intake or evidences of other chronic liver diseases (e.g., viral, autoimmune or metabolic, etc.). Anthropometric, laboratory and radiologic data were collected, including vibration-controlled transient elastography (VCTE) and body composition analysis (BCA) at the time of enrollment.Patients visited to the clinic regularly for comprehensive interview and laboratory tests every 3-6 months and underwent VCTE and BCA on a yearly basis, under individualized lifestyle intervention including reduced calorie intake and moderate-intensity exercise.

Results: As of March 2019, 63 patients out of the entire prospective cohort (n = 272) were included in the analysis who completed follow-up evaluation including paired measurements of VCTE and BCA. Median age was 48.9 years, and 44 patients were male (69.8%). Baseline body mass index (BMI) was 26.5 kg/m^2 (median; intertquartile range [IQR], 24.5–29.9); 20 patients had BMI<25 (nonobese, 31.8%), and 43 had BMI≥25 (obese, 68.3%), respecitvely. At baseline, metabolic syndrome (MetS) was found in 33 patients (52.4%). Baseline AST/ALT were 36 IU/L (26–60) and 51 IU/L (31–126). Baseline controlled attenuation parameter(CAP) was 293.4±42 dB/m andliver stiffness measurement(LSM) was 7.46 kPa(range, 3.30–21.3). During follow-up, mean LSM decreased from 7.46±3.22 kPa to 4.76±1.53 kPa (*P* < 0.001); in the meantime, changes in BMI, percentage fat/weight (PF/Wt), and appendicular skeletal muscle/weight (ASM/Wt) were -0.47 (*P* = 0.005), -2.36 (*P* < 0.001), and +0.56 (*P* = 0.002), respectively. Multivariate logistic regression analysis showed that increased number of MetS components during follow-up was significantly associated with ΔPF/Wt (odds ratio [OR] = 1.309; 95% confidence interval (CI), 1.032–1.660; *P* = 0.027), and ΔASM/Wt (OR = 0.597; 95% CI, 0.245-0.931; *P* = 0.030). Significant change in HOMA-IR during follow-up was observed in the nonobese group (-0.54; IQR, -0.83–-0.20; *P* = 0.031), but not in the obese group (-0.08; IQR, -2.62–1.17; *P* = 0.539).

Conclusions: In this preliminary report of a prospective cohort study, changes in BMI under lifestyle intervention led to decrease in LSM, along with reciprocal changes in percentage fat and relative skeletal muscle mass, along with components of metabolic syndrome in NAFLD patients. Improvement in the insulin resistance was more profound in the nonobese group rather than the obese group.

Keywords: Nonalcoholic fatty liver disease, Lifestyle intervention, Body composition, Insulin resistance

Liver Cancer, Basic

PE-181

Dickkopf-1 from Hepatocellular Carcinoma Cells Promotes the Angiogenic Potential of Endothelial Cells by Activating the VEGFR-2 Signaling Pathway

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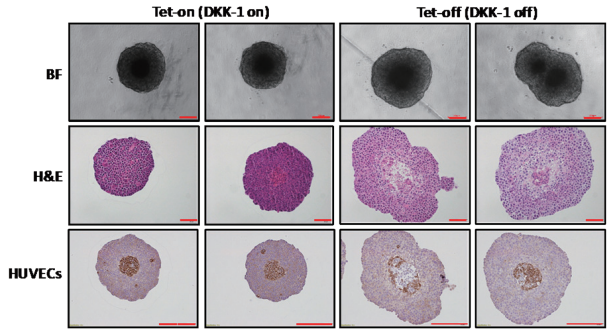
Aims: Dickkopf-1 (DKK-1) is an antagonist of Wnt signaling. Several reports have shown an association between the elevated expression of DKK-1 and tumor angiogenesis. However, the biological function of DKK-1 in angiogenesis of hepatocellular carcinoma (HCC) is not well documented. We investigated the phenotypical changes of vascular endothelial cells after interactions with HCC cells expressing DKK-1 using two-dimensional (2D) and three-dimensional (3D) co-culture systems.

Methods: The cell lines Huh7 and Hep3B, with low and high DKK-1 expression, respectively, were selected. The tetracycline-inducible DKK-1 expression cell line (Tet-on Huh7) and a DKK-1 knockout cell line using CRISPR/Cas9 (KO Hep3B) were established. The angiogenic potential of human umbilical vein endothelial cells (HUVECs) was investigated using wound scratch, transwell, and tube formation assays. HUVECs were co-cultured with Tet-on/off Huh7, or KO Hep3B for 3D spheroid

models, where cells were seeded in a 10:1 ratio (HCC cells:HUVECs) in non-adhesive, round-bottom 96-well plates. After 3 days, spheroids were harvested for quantitative polymerase chain reaction, western blotting, and immunohistochemistry staining.

Results: The angiogenic potential of HUVECs significantly increased after being treated with human recombinant DKK-1. When HUVECs were treated with Tet-on/off Huh7 and KO Hep3B-conditioned media in an indirect 2D co-culture system, Tet-on Huh7 increased the angiogenic potential of HUVECs, which was not increased with Tet-off Huh7 and KO Hep3B. When 3D spheroids were constructed to mimic the *in vivo* environment, spheroids with HUVECs and Tet-on Huh7 were constructed faster and more packed than those mixed with Tet-off Huh7. When HUVECs in spheroids were stained, HUVECs mixed with Tet-on Huh7 cells exhibited greater viability than those mixed with Tet-off Huh7 cells (Figure). The biological morphology of spheroids with KO Hep3B was similar to those with Tet-off Huh7. Furthermore, the expression levels of vascular endothelial growth factor receptor 2 (VEGFR-2) signaling factors significantly increased when HUVECs were mixed with Tet-on Huh7 cells in 3D spheroids.



Dickkopf-1 (DKK-1), Tetracycline (Tet), Bright-field (BF), Hematoxylin and Eosin(H&E) staining, Immunohistochemistry staining of CD31 for HUVECs, Scale bar indicates 200 μm

Conclusions: We confirmed that DKK-1 from HCC cells promoted the angiogenic potential of HUVECs by activating the VEGFR-2 signaling pathway. Thus, further studies should determine whether blockade of DKK-1 may represent a novel therapeutic target for HCC treatment.

Keywords: Hepatocellular carcinoma, Angiogenesis, 3 dimention culture

PE-182

Protective Effect of Bioengineered Silver Nanoparticles against Diethylnitrosamine Induced Hepatocarcinogenesis via Knockdown of Oxidative Stress and Inflammation by Regulating NF-κB Pathway

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Aims: Current study was designed to biofabricate, characterize and evaluate protective effect of *Trianthema portulacastrum* (TP) extract mediated silver nanoparticles (AgTPNPs) against diethylnitrosamine (DEN) induced hepatocarcinoma in rat model.

Methods: Liver damage in rats was induced with a single dose of DEN (200 mg/kg) as well as double dose of phenobarbital. Simultaneously, animals were administered with AgTPNPs at two dose levels (10 and 20 mg/kg p.o.) for 16 weeks. At the end of study, serum biomarkers, hematological status, antioxidants enzymes, proinflammatory cytokines, i.e., tumor necrosis factor-α, interlukin-6, interlukin-1β, and nuclear factor kappa beta (NF-kB), were examined to assess the protective effect of AgTPNPs. Additionally, gene expression (*Akr1b10, Foxp1* and *ING3*) concerned with hepatocarcinoma as well as was as histological studies were also undertaken to assess the outcomes of current study.

Results: AgTPNPs were synthesized by co-precipitation method and different characterization techniques confirmed the formation of spherical crystalline nanoparticles with size range of 50-80 nm. FTIR results showed the existence of possible bioactive functional groups of phytoconstituents in the synthesized AgTPNPs. Results demonstrated that DEN significantly induced the hepatocellular carcinoma in each group, which was significantly reversed ($P < 0.001$) by AgTPNPs in a concentration dependent manner. A significant reduction in level of serum hepatic and non-hepatic marker enzymes, oxidative stress and different inflammatory markers via direct and indirect inhibition of NF-kB expression were observed in rats administered with AgTPNPs. Regarding gene expression, AgTPNPs treated group exhibited significant elevation in *Akr1b10* and *ING3* expression whereas reduction in *Foxp1* gene expression level as compared to control group. Histopathological study further favored the restructuring effect on destructed hepatic tissue.

Conclusions: Collectively, results demonstrated that AgTPNPs potentially ameliorated the damaging effects of DEN induced hepatocellular carcinoma and it can be utilized as an effective nano technology based anticancer approach.

Keywords: Liver Cancer, Biofabricate, Nanoparticles, Histological

PE-183

Effect of Virtual Reality and Training on Liver Operation Planning

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Aims: The three-dimensional relation of a liver tumour to the intrahepatic vascular trees is basis of operation planning in liver surgery. Yet it has not been proven whether 3D reconstruction and further computerised processing will enhance precision of operation planning in liver surgery which has been based on the liver segment classification of Couinaud up to now.

Methods: Our interdisciplinary group has developed a new interactive computer-based quantitative 3D operation planning sys-

tem for liver surgery which is being introduced into the clinical routine. The system quantifies the organ structures semiautomatically, defines resection planes depending on safety margins and the vascular trees, and presents the data in digital movies as well as in quantitative reports. We conducted a clinical trial to evaluate whether 3D reconstruction will lead to an improved operation planning. Data of 7 virtual patients were presented to a total of 81 surgeons in different levels of training. The tumours had to be assigned to a liversegment and subsequently drawn together with the operation proposals into a liver model. The precision of both was measured quantitatively for each surgeon and stratified concerning 2D and different types of 3D presentations.

Results: The 3D anatomy can be visualised in high quality which results in good perception of the third dimension (depth). Tumour assignment to liver segments was significantly correlated to the level of training ($P < 0.05$). There was a significant increase ($P < 0.001$) in the precision of tumour localisation by 51% and resection proposal from 2D through 3D reconstructions by 13%-21%. Quantitative differences of the simplified Couinaud's classification of the liver segments compared to the true vascular anatomy of up to 40% were found.

Conclusions: The impact of individual 3D-reconstruction on surgical planning has been proven to be significant and increases precision quantitatively.

Keywords: 3D reconstruction, Liver segment, Tumors, Vascular tree

PE-184

Alpha-Fetoprotein Inhibition Enhances the *in Vitro* and *in Vivo* Anti-Tumor Effects of Sorafenib on Hepatocellular Carcinoma

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Aims: Sorafenib is the standard systemic therapy for patients with advanced hepatocellular carcinoma (HCC); however, the drug has moderate response rate and duration, and low disease control rate. Moreover, the survival rate, after administration of sorafenib, is lower in patients with high serum alpha-fetoprotein (AFP) levels. Thus, we hypothesized that AFP inhibition increases the anti-tumor effect of sorafenib on HCC in *in vitro* and *in vivo* models.

Methods: AFP-producing Huh-7 cell line was used in this study. The cells were transfected with AFP siRNA for 72 hours followed by treatment with sorafenib (2 μmol/L) for 24 hours. Hoechst 33342 staining was used to analyze cell number using cytation3. Propidium iodide staining was used to assess cell cycle state using flow cytometry. Immunoblotting assay was used to determine apoptosis. Patient-derived xenograft (PDX) models were used to evaluate augmentation effects of AFP inhibition on sorafenib. PDX models were divided into 5 groups for treatment with the following: control; non-target siRNA; AFP siRNA; sorafenib; AFP siRNA + sorafenib. siRNA was intratumorally injected every 3 days and sorafenib (10 mg/kg) was administered orally by gavage once daily. At the end of study, the body weights of the mice were recorded, and the mice were sacrificed their tumors were harvested for analysis.

Results: AFP siRNA inhibited AFP production in HCC cells and also inhibited their proliferation. Inhibition of HCC cell proliferation was greater when treated with both AFP siRNA and sorafenib than when treated with sorafenib or AFP siRNA alone. Sorafenib increased the percentages of Huh-7 cells in the sub-G0/G1 phase; the sub-Go/G1 population was enhanced in AFP-siRNA transfected Huh-7 cells. Cells treated with both AFP siRNA and sorafenib showed increased apoptosis via upregulation of caspase3 and PARP cleavage compared with cells treated with sorafenib alone. In the PDX model, treatment with AFP siRNA and sorafenib significantly inhibited subcutaneous HCC tumor growth in comparison with treatment with sorafenib alone.

Conclusions: AFP suppression augments the anti-proliferative effect of sorafenib in human HCC cells. These results suggest that AFP inhibition may play a synergistic role in the anti-tumor effect of sorafenib in patients with advanced HCC.

Keywords: Hepatocellular carcinoma, Sorafenib, Alpha-fetoprotein, Augmentation effect

PE-185

Successful Single-Stage Extended Right Hemihepatectomy with Low Anterior Resection of the Rectum in Patients with Colorectal Cancer with Liver Metastases

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Aims: Colorectal cancer (CRC) occupies the 4th place in the structure of cancer morbidity in Kazakhstan. From 35 to 57% of patients with colorectal cancer with primary treatment have metastases to the liver. However, active surgical treatment of metastatic liver invasion allows achieving 5-year survival in 27-47% of patients.

Methods: We present the clinical observation of successful surgical treatment of rectal cancer with liver metastases with simultaneous execution of extended right hepatectomy and "low" anterior rectal resection. Patient I., 52 years old, male. From anamnesis: the above complaints are noted within 6 months. Ultrasonography of the abdominal cavity revealed a focal lesion in the right lobe of the liver, with a colonoscopy: in the middle-ampullar rectal section, a tumor up to 5 cm in length is located 8 cm above the anus, which closes the colon lumen of the gut by 2/3; the result of a biopsy: moderately differentiated adenocarcinoma. By PET – no other metastatic problems.

Results: Was performed extended right hepatectomy (cholecystectomy) and "low" anterior rectal resection. After operation

recommended adjuvant chemotherapy. At the control examination 3 months later after the operative treatment the condition is satisfactory, the laboratory parameters are within the norm. With ultrasound of the abdominal cavity signs of progression of the disease is not revealed.

Conclusions: Thus, the using of one-step operations on the primary tumors of CRC and liver metastatically lesions makes it possible to perform the surgical treatment in a shorter time and earlier to start adjuvant chemotherapy. With hepatic metastases of CRC, it is justified to perform extended liver resections.

Keywords: Liver metastasis, CRC, Hemihepatectomy, Single-satge

PE-186

Significance of Plasma Levels of Soluble Programmed Death-1 and Soluble Programmed Death-Ligand 1 in Hepatocellular Carcinoma

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Aims: In contrast to tissue expression of programmed death-1 (PD-1) and its ligands (PD-L1), plasma levels of soluble programmed death-1 (sPD-1) and soluble PD-L1 (sPD-L1) were not clearly defined in hepatocellular carcinoma (HCC). This study aimed to investigate plasma levels of sPD-1 and sPD-L1, and to evaluate their relationship with clinical factors and overall survival in HCC patients.

Methods: Using plasma samples obtained from the prospectively enrolled HCC patients (n = 242) and age-and sex-matched healthy controls (n = 91), the plasma levels of sPD-1 and sPD-L1 were measured by commercial ELISA.

Results: The 242 HCC patients showed a mean age of 60.8 years, male in 80.6%, HBsAg-positive in 70.2%, Child-Pugh class A in 84.7%, and BCLC 0/A in 57.0%. The plasma sPD-1 was detected in 35.2% of healthy control (median level, 244; IQR, 92–1948 pg/mL) and in 34.7% of HCC patients (median level, 472; IQR, 177–1660 pg/mL; $P = 0.25$). In healthy control group, sPD-1 level was higher in male than in female patients ($P = 0.03$). The plasma sPD-L1 was detected in almost all the subjects, and not different between heathy control and HCC group (median 371 versus 332 pg/mL, $P = 0.13$). The proportion of Child-Pugh class B was higher in detectable-sPD-1 group (22.6%) than in the non-detectable-sPD-1 group (14.4%, $P = 0.04$), and higher in the high-sPD-L1 group (19.8%) than in the low-sPD-L1 group (9.9%, $P = 0.04$). Otherwise, there was no clinical factor significantly associated with sPD-1 level and sPD-L1 level. During mean follow-up of 3.5 years, the overall survival was not different between the non-detectable- and detectable-sPD-1 group, and between the low- and high-sPD-L1 group.

Conclusions: Though, detectable sPD-1 level or high sPD-L1 level were associated with poor liver function in HCC patients, either level may not be a useful biomarker for the diagnosis or prognosis of HCC.

Keywords: Plasma level, Soluble programmed death-1, Soluble programmed death-ligand 1, Hepatocellular carcinoma

PE-187

Significance of Plasma Levels of Angiopoietin-2 and Vascular Endothelial Growth Factor in Hepatocellular Carcinoma

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Aims: This study aimed to investigate the profiles of plasma levels of Angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF), and to elucidate their association with the overall survival in hepatocellular carcinoma (HCC) patients.

Methods: Using the plasma samples obtained from the prospectively enrolled HCC patients (n = 242) and age- and sex-matched healthy controls (n = 91), the plasma levels of Ang-2 and VEGF were measured by commercial ELISAs.

Results: The HCC patients showed a mean age of 60.8 years, male in 80.6%, HBsAg-positive in 70.2%, Child-Pugh class A in 84.7%, and BCLC stage 0/A in 57.0%. Compared to healthy controls, HCC patients showed a significantly higher Ang-2 level (median 487 versus 1684 pg/mL, $P < 0.001$) and higher VEGF level (median 4.2 versus 26.5 pg/mL, $P < 0.001$). Using the median level as a cutoff, the high-Ang-2 group (n = 120) showed a significantly poorer performance, poorer liver function, more aggressive tumor features, and lower survival than the low-Ang-2 group. In contrast, the high-VEGF group (n = 120) showed a significantly poorer performance and more aggressive tumor features than the low-VEGF group, but liver function and survival were not different from the low-VEGF group. On multivariate analysis, the high-Ang-2 level was an independent factor (HR [hazard ratio] 2.51; 95% CI [confidence interval] 1.60–3.94; $P < 0.001$) associated with the overall survival, along with Child-Pugh class B (HR 3.51; 95% CI, 2.21–5.59; $P < 0.001$) and TNM stage 3 or 4 (HR 5.41; 95% CI 3.31–8.85). Moreover, the AUROC of Ang-2 (0.749) for the survival prediction, was higher than that of alpha-fetoprotein

(0.717) or PIVKA-II (0.743).

Conclusions: Plasma level of Ang-2 in HCC was an independent factor for overall survival, showing a higher AUROC than alpha-fetoprotein, while VEGF plasma level was not associated with survival in HCC. Further validation study is warranted.

Keywords: Plasma level, Angiopoietin-2, Vascular endothelial Growth factor, Hepatocellular carcinoma

PE-188

Cytotoxicity of Human Hepatic Intrasinusoidal CD-56bright Natural Killer Cells against Hepatocellular Carcinoma Cells

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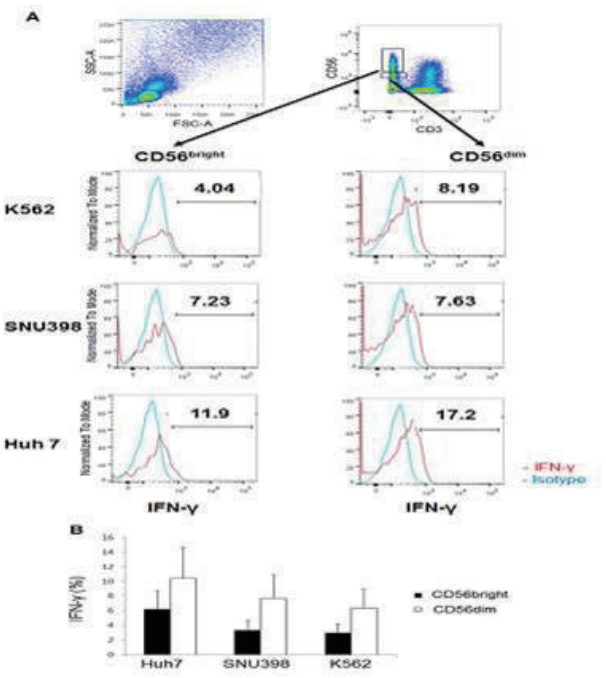
Aims: Hepatic intrasinusoidal (HI) natural killer (NK) cells from liver perfusate have unique features that are similar to those of liver-resident NK cells. Previously, we have reported that HI CD56^{bright} NK cells effectively degranulate against SNU398 hepatocellular carcinoma (HCC) cells. Thus, the aim of this study was to further investigate the phenotype and function of HI NK cells.

Methods: Healthy living donor right lobe graft was washed with 1 L of histidine-tryptophan-ketoglutarate solution, and liver perfusate was collected. Various fluorescence-labeled Abs were used for flow cytometry. K562, Huh7, or SNU398 cells as target cells were seeded in round-bottom 96-well plates at 7000 cells/well. CytoTox 96 Non-radioactive cytotoxicity assay was performed.

Results: We found that HI CD56^{bright} NK cells degranulated much less to Huh7 cells. HI CD56^{bright} NK cells expressed NKG2D, NKp46, TNF-related apoptosis-inducing ligand (TRAIL), and FAS ligand (FASL) at higher levels than CD56^{dim} cells. SNU398 cells expressed more NKG2D ligands and FAS and less PD-L1 than Huh7 cells. Blockade of NKG2D, TRAIL, and FASL significantly reduced the cytotoxicity of HI NK cells against SNU398 cells, but blockade of PD-L1 did not lead to any significant change. However, HI NK cells produced IFN-γ well in response to Huh7 cells.

Conclusions: The cytotoxicity of HI CD56^{bright} NK cells was attributed to the expression of NKG2D, TRAIL and FASL. These results suggest the possible use of HI NK cells for cancer immunotherapy and pre-screening of HCC cells to help identify the most effective NK cell therapy recipients.

Keywords: Hepatic intrasinusoidal NK cells, Liver-associated NK cells, Cancer immunotherapy, Cytotoxicity



PE-189

Laparoscopic Hemihepatectomy at Liver Tumors

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Aims: From 2015 to 2018 in Kyzylorda Regional Medical center performed 15 laparoscopic right-sided hemihepatectomy, laparoscopic segmentectomy II and III grade and laparoscopic segmentectomy V—VI art.

Methods: From 2015 to 2018 at the present time performed 15 laparoscopic liver surgery: segmentectomy II, III degree, laparoscopic bisegmentectomy IV—V degree and 4 laparoscopic right-sided hemihepatectomies When performing a right hemihepatectomy endoscopic instrument LigaSure complex "Force Triad" enables reliable control of hemostasis at the intersection of the short hepatic veins, stepby-step dissection of the liver parenchyma, crossing the parenchyma in the hepatic branches of the portal vein. The apparatus ENDO GIA 30 was stitched and crossed the right hepatic vein. The resected fragment of the liver was loaded into a container and evacuated through the incision in the right iliac region. The surface of the liver was covered with hemostatic mesh "Surgicel".

Results: In right-sided hemigepatectomy surgery duration was from 150 to 240 min, blood loss of 150-400 ml. in liver resection and bisegmentectomy intervention lasted 90-120 min, and blood loss was 60-80 ml. Postoperative analgesia was provided by a constant epidural infusion of 1% lidocaine. On the second day after the operation, the patients were transferred to the Department in a satisfactory condition. Separated by drains did

not exceed 80 ml per day. The drainages were removed on the 2-3 days. Activation for 1-3 days.

Conclusions: The Obtained results allow to conclude that video surgery of large volume on the liver has great prospects in clinics where there is sufficient experience of such surgical interventions in an open manner.

Keywords: Laparoscopic, Hemihepatectomy, Liver, Tumors

PE-190

Serum Level of Growth Differentiation Factor 15 Reflects the Aggressiveness of Hepatocellular Carcinoma Including Metastasis

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Aims: Growth differentiation factor (GDF15) is one of the transforming growth factor β superfamily and increased in several cancers including hepatocellular carcinoma (HCC). However, the level of GDF15 according to the characteristics of HCC has not been investigated. We examined the serum level of GDF15 in HCC patients and correlated with the clinical tumor characteristics.

Methods: A total of 80 patients diagnosed with HCC between 2013 and 2017 were analyzed in our study. In 80 enrolled patients, 20 patients for each modified UICC stage (I-IV) were included. The 15 healthy patients were also included as control group. The serum level of GDF15 and programmed death-1 ligand 1 (PD-L1) were checked at the time of initial diagnosis of HCC. The level of GDF15 were analyzed with tumor characteristics including tumor stage, size, presence of portal vein thrombosis (PVT) and metastasis.

Results: The mean age of 80 HCC patients were 59.9 years and 54 patients (67.5%) were HBV-related HCC. The median level of GDF15 and PD-L1 were 782.7 pg/mL (range, 624.1-909.1) and 35.4 pg/mL (range, 15.7-63.4), respectively. The serum level of GDF15 were significantly higher in HCC patients than healthy control ($P < 0.001$). However, PD-DL1 level were significantly lower in HCC patients ($P = 0.001$). Moreover, advanced stage (III-IV) had higher level of GDF15 than stage I-II ($P < 0.05$) and PD-L1 level were not differ between tumor stage. The size of tumor had a significantly positive correlation with the level of GDF15 ($r = 0.50$, $P < 0.001$). The patients with metastasis or PVT had higher GDF15 level with significance ($P < 0.003$; $P = 0.001$, respectively).

Conclusions: The serum level of GDF15 is high in HCC patients and higher level represent the aggressiveness of HCC including tumor size, PVT and metastasis.

Keywords: Growth differentiation factor 15, Hepatocellular carcinoma, Metastasis, Portal vein thrombosis, Tumor size

PE-191

Hydralazine Stimulates HIF-1-Dependent but Inhibits HIF-2-Dependent Gene Expression in Liver Cancer Cells

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Aims: Hypoxia-inducible factors (HIFs) are transcriptional regulators that mediate the cellular response to low oxygen. Although HIF-1 is usually considered as the principal mediator of hypoxic adaptation, several tissues and different cell types express both HIF-1 and HIF-2 isoforms under hypoxia or when treated with hypoxia mimetic chemicals such as Hydralazine. However, the similarities or differences between HIF-1 and HIF-2, in terms of their tissue- and inducer-specific activation and function, are not adequately characterized.

Methods: To address this issue, we investigated the effects of true hypoxia and hypoxia mimetics on HIF-1 and HIF-2 induction and specific gene transcriptional activity in two hepatic cancer cell lines, Huh7 and HepG2.

Results: Both hypoxia and Hydralazine caused rapid induction of both HIF-1α and HIF-2α proteins. Hypoxia induced erythropoietin (EPO) expression and secretion in a HIF-2-dependent way. Surprisingly, however, EPO expression was not induced when cells were treated with Hydralazine. In agreement, both HIF-1- and HIF-2-dependent promoters (of PGK and SOD2 genes, respectively) were activated by hypoxia while Hydralazine only activated the HIF-1-dependent PGK promoter. Unlike Hydralazine, other hypoxia mimetics such as DFO and DMOG activated both types of promoters. Furthermore, Hydralazine impaired the hypoxic stimulation of HIF-2, but not HIF-1, activity and Hydralazine-induced HIF-2α interacted poorly with USF-2, a HIF-2-specific co-activator.

Conclusions: These data show that, despite similar induction of HIF-1α and HIF-2α protein expression, HIF-1 and HIF-2 specific gene activating functions respond differently to different stimuli and suggest the operation of oxygen-independent and gene- or tissue-specific regulatory mechanisms involving additional transcription factors or co-activators.

Keywords: Liver, Cancer

PE-192

Targeting HDAC2 Elicits Synergistic Anti-Cancer Effects of Sorafenib in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the fifth frequently diagnosed cancer and is the second leading cause of cancer death worldwide. Many groups have suggested possible clinical applications for liver cancer therapy but sorafenib, an orally-available kinase inhibitor, is the only standard systematic therapeutics for treatment of hepatocellular carcinoma. However, survival benefit of sorafenib is unsatisfactory due to high level heterogeneity of individual response. We previously reported that histone deacetylase 2 (HDAC2) was deregulated in HCC, and thereby contributed to liver tumorigenesis by enhancing mitotic and metastatic potential of transformed cells. Targeted-disruption of HDAC2 suppressed *in vitro* and *in vivo* tumorgigenic potential of HDAC2 in liver cancer. The goal of this study was to investigate whether both sorafenib treatment and HDAC2 inhibition elicit synergistic anti-tumor effect against HCC cells.

Methods: A series of inhibitors, activators and siRNAs was utilized to validate regulatory mechanisms for HDAC2-targeting in hepatocelluar carcinogenesis.

Results: Here, we showed that sorafenib effectively blocked ERK/MEK and AKT signaling pathway upon EGF stimulation in liver cancer cell lines. Also, we found that valproic acid (VPA), a selective inhibitor of histone deacetylase family I, and sorafenib treatment synergistically evoked liver cancer cell growth retardation. This effect was recapitulated by HDAC2 knockdown with sorafenib treatment and exhibited synergistic effect on apoptotic cell death of liver cancer cell lines, Hep3B and Huh7, compared to single treatment of sorafenib.

Conclusions: Our data suggest that combined sorafenib treatment with HDAC2 targeting may provide more benefits toward HCC therapy providing a novel approach for future application in patients with advanced HCC.

Keywords: Histone deacetylase 2, Sorafenib, Valproic acid, Hepatocellular carcinoma

PE-193

Association of Telomerase Reverse Transcriptase Gene Expression with Clinical Phenotype of Hepatocellular Carcinoma

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Aims: Cancer driver genes and major pathways leading to liver carcinogenesis have yet to be elucidated. As a gatekeeper mutation, telomerase reverse transcriptase (TERT) was recently identified to have a fundamental role in multi-step hepatocarcinogenesis. This study aimed to investigate the association between TERT gene set analysis and clinical phenotype of HCC.

Methods: The protein-protein interaction (PPI) networks were established for TERT through the STRING database, after which potential genes related to HCC or apoptosis were finally detected. We examined the expression of the selected gene set by qRT-PCR in tissue samples of 153 patients with HCC (111 paired surgical and 42 non-surgical specimens). The data were correlated with tumor stage, recurrence, and progression of HCC.

Results: From the PPI network, seven TERT gene sets for HCC, such as CCT5, TUBA1B, mTOR, RPS6KB1, AKT1, WHAZ, YWHAQ, and TERT, were identified and analyzed for gene expression by qRT-PCR. Among these, TERT was the most significant differentially expressed gene; the expression of TERT is upregulated in tumor than non-tumor tissues, with its increasing expression with tumor stage progression. Patients with a high expression of TERT had significantly higher rates of recurrence and worse progression-free survival than those with a low TERT expression. Upregulation of TERT expression was significantly associated with male patients.

Conclusions: TERT gene expressions are associated with clinical phenotype of HCC, in terms of the development, recurrence, and disease progression of HCC. Our data indicate that TERT pathway might serve as a useful surrogate for the follow-up of HCC patients.

Keywords: Telomere, Hepatocellular carcinoma, Biomarker, Progression

PE-194

Investigating Role of Cinnamon Bioactive Compounds Towards Hepatic Carcinoma Marker in Diabetes State Using Computational Interaction Approach

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Jaypee Institute of Information Technology, NOIDA, INDIA

Aims: Investigating role of Cinnamon bioactive compomnds towards hepatic carcinoma marker in diabetec state using computational interaction approach. The aberration in c-Met kinase (PDB ID: 2RFN) is because of overexpression and mutation and to trigger the carcinogenic pathways associated with HCC reported in approximately 50% of patients and also exhibited the relations with insulin-like growth factor receptor 1, Thus the c-Met inhibition may be one of the potential therapeutic approach and may play important role in the control or inhibition of HCC. Traditionally in indina system *Cinnamomum cassia* as

a spice has been used in food preparation and therapeutically reported to have anti cancer activities in literature.The active compound Cinnamaldehyde, cinnamic acid, and cinnamyl alcohol have been found in *Cinnamomum cassia.*

Methods: Here in this work investigate the computational intection study using autodock tool *with* Cinnamaldehyde and observed the interaction with c-met pdb Id 2RFN. (1) first download the PDB structure of c met protein from RCSB web portal PDB ID 2RFN (2) Performed the docking experiment using autodock vina ver 1.1.2 (blind docking) on biological assembly 1 out of two of the molecule in the structure wit all default parameter (3) the results has been noticed and interaction is studied.

Results: The docking score was found -4.1 K Cal/mol.

Conclusions: We performed the basic interaction of the selected compound and found good interaction can be further validated simulation study. This gives an idea of about the insight of mechanism of action of these compound.

Keywords: C Met, Docking, Diabetes, Cinnamomum cassia

PE-195

Adipose Tissue-Derived Mesenchymal Stem Cells Inhibit Hepatocellular Carcinoma Cells via Secretion of Interferon (IFN)-Beta and Tumor Necrosis Factor–related Apoptosis-Inducing Ligand (TRAIL) *in Vitro*

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Aims: Adipose tissue-derived mesenchymal stem cells (ASCs) are emerging as promising anti-agents to inhibit hepatocellular carcinoma because the interferon (IFN)-beta and tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) secreted by ASCs inhibits certain cancer cells through decreasing tumor cell growth and inducing apoptosis separately. However, it was not investigated that ASCs inhibit hepatocellular carcinoma cells through IFN-beta and TRAIL *in vitro*. Therefore, it was hypothesized that ASCs suppress hepatocellular carcinoma cell through IFN-beta and TRAIL.

Methods: In order to test the hypothesis, Huh7 and Hep3B human hepatocellular carcinoma cells were co-cultured with ASCs for 5 days. After co-culture with ASCs, the Huh7 and Hep3B cells were examined for cell viability using MTT assay. In addition, Huh7 and Hep3B cells were individually treated with concentrated media (CM) obtained from supernatant of cultured ASCs for 4 days with or without neutralizing antibody to IFN-beta and/or TRAIL so as to determine effects of IFN-beta and/or TRAIL in decreased cell viability of the Huh7 and Hep3B cells co-cultured with ASC.

Results: Results of experiments showed that cell viability of Huh7 and Hep3B cells indirectly co-cultured with ASCs was decreased compared to control group. In addition, Huh7 and Hep3B cells were individually treated with concentrated media (CM) obtained from supernatant of cultured ASCs for 4 days with or without neutralizing antibody to IFN-beta and/or TRAIL. It was observed that cell viability of the Huh7 and Hep3B cells treated with ASC-CM was decreased. Huh7 and Hep3B cells co-treated with ASC-CM and neutralizing antibody to IFN-beta or TRAIL showed increased cell viability compared to Huh7 and Hep3B cells treated with ASC-CM alone.

Conclusions: We conclude that ASC may play a role in inhibiting hepatocellular carcinoma through IFN-beta and TRAIL.

Keywords: Adipose tissue-derived mesenchymal stem cell, Hepatic cancer, IFN-beta, TRAIL

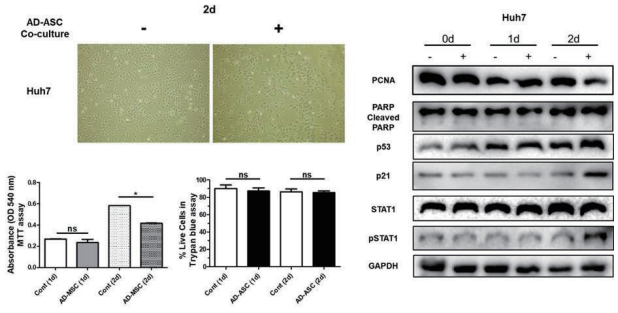

Figure 1.

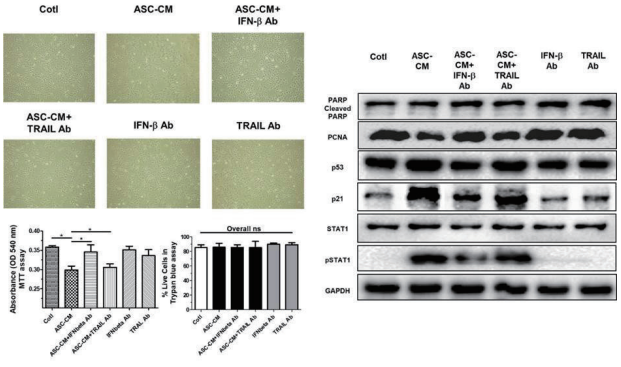

Figure 2.

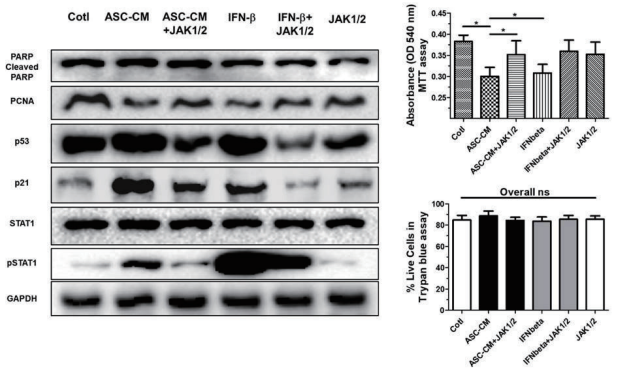

Figure 3.

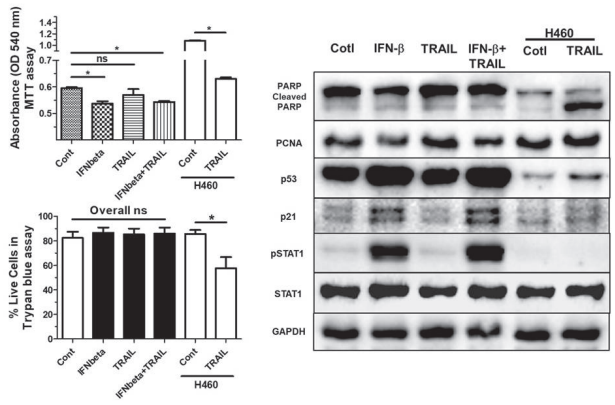

Figure 4.

PE-196

Radiofrequency Ablation of Metastatic Liver Tumors

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Aims: Metastatic liver cancer is one of the most dangerous conditions during the course of cancer. The most common liver metastases occur in colorectal cancer, breast cancer, stomach. Currently, the method of radiofrequency ablation (RFA) is increasingly used as an alternative to surgery. This method of local exposure allows the thermal destruction of the tumor under the influence of high-frequency radio emission. The RFA method is used both in the presence of a solitary focus in the liver, and in single foci located in one lobe of the liver, and in both lobes. The technique is used both for small metastases up to 3 cm in size and for large formations up to 5 cm in size.

Methods: RFA of liver metastatic foci was performed in 6 patients, including 3 men and 4 women. To conduct RFA was used the generator of the company "Medtronic (COVIDIEN)" and single needle electrodes "Cool-Tip" with a length of 25 cm, with working parts of 30 mm Ultrasonic testing was carried out on the scanner HITACHI ARIETTA V70, the positioning of the electrode in the center was carried out using convex probe with a scanning frequency of 3.5 MHz. We used percutaneous access to the hearth by the method of free hand. All RFA sessions were performed in the mode of "Impedance control", in which the impact power is automatically adjusted depending on the resistance of the tissue and is 150-170 watts. The duration of the application was standard and averaged 12 minutes.

Results: In dynamic observation within 12 months after RFA continued growth was detected in 3 cases, stabilization of metastatic process in the liver was observed in 4 cases. It is noted that the size of metastatic foci, not exceeding 2 cm, in no case was not recorded continued growth. Continued growth was identified in those cases where the size of metastatic foci greater than 3, see Method PET-CT demonstrated the highest informativeness among all control methods.

Conclusions: The Findings suggest that RFA is an effective method of treatment of patients with metastatic liver cancer of various primary locations. The main advantage of this technique is minimally invasive, and as a result, short periods of hospitalization.

Keywords: Liver, Tumors, HCC, RFA

PE-197

Transarterial Chemoembolization for Primary and Metastatic Liver Tumors

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Aims: To assess effectiveness of chemoembolization of hepatic artery (CEHA) in treatment of patients with metastatic colorectal cancer, and also to determine the optimal interval in combination of CEHA with other treatment methods.

Methods: The study includes analysis of the results of treatment of 30 patients with resectable metastases of colorectal cancer in the liver. The first group included 15 patients with resection made 1 week after CEHA. The second group consisted of 15 patients in whom resection operation was made 2 weeks after CENA with subsequent assessment of morphological changes in metastases.

Results: Therapeutic pathomorphism was recorded in 25/30 patients. In the first group, therapeutic pathomorphism was observed in 13/15 patients. In 11/13 patients, the 2nd degree of therapeutic pathomorphism was recorded. In 2/13 patients – the 1st degree. In the second group, therapeutic pathomorphism was observed in 12/15 patients. In all patients the 2nd degree of therapeutic pathomorphism was recorded. No significant differences in the degree of therapeutic pathomorphism were recorded on the 7th and 14th day after regional chemotherapy ($P = 0.436$).

Conclusions: Hepatic artery chemoembolization is an effective method of treating patients with metastases of colorectal cancer in the liver. In use of chemoembolization of hepatic artery in combination with other surgical methods, the seven-day time interval is optimal.

Keywords: CEHA, Liver, Treatment, Tumor

PE-198

Activated Human Hematopoietic Stem Cells Exhibit Antitumor Activity toward Hepatocellular Carcinoma *in Vitro*

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Aims: Hepatocellular carcinoma (HCC) recurrence rate after liver transplantation (LT) consists of 10%-20% and remains the leading cause of cancer-related death. We have successfully applied an adoptive immunotherapy to liver cirrhotic patients with HCC in a phase I trial after LT. In our study we have shown that Interleukin (IL)-2/OKT3 stimulated lymphocytes, containing much of NK (natural killer)/NKT cells, from donor liver graft, have a vigorous anticancer effect. However, a single treatment with activated lymphocytes might lead to limited effects. We aimed to develop a new therapeutic approach for the efficient expansion of such innate components of cellular immunity obtained from the circulated hematopoietic stem cells (HSCs).

Methods: Human HSCs were cultured for 14 days in the presence of 5% AB-serum X-VIVO15 medium containing IL-7, IL-15, Flt3L (Fms-related tyrosine kinase 3 ligand), stem cells factor (SCF). Furthermore, the expanded cells were briefly (72 hours) pre-activated with IL-12 and IL-2 before the harvest. The phenotype and characterization of activated cells were identified by flow cytometric analysis and the cytotoxicity against tumor was determined by ^{51}Cr release assay.

Results: After being cultured for 17 days the proportion of cell fractions in the expanded HSCs varied among individuals. The average proportion of $CD56^+CD3^-$, $CD56^+CD3^+$ and $CD56^-CD3^+$ was 15.4% (range, 3.1%-39.7%), 10% (range, 2.2%-37%) and 58.4 (range, 17.9%-91.8%), respectively. The brief pre-activation of expanded HSCs exhibit enhanced expression of IFN-γ, TNF-α, Granzyme B and TNF-related apoptosis-inducing ligand (TRAIL) on their surface. Furthermore, these cells showed vigorous anticancer ability *in vitro*, at an effector-target cell ratio of 40:1, NK cells destroyed 63% (±10.1) of HepG2, an HCC cell line.

Conclusions: These findings suggest that repeated adoptive immunotherapy using activated human HSCs might be a promising approach for inducing innate immunity to decrease the incidence of cancer recurrence after liver transplantation.

Keywords: Liver, Cancer, Transplantation

PE-199

Association between Body Mass Index and Postoperative Morbidity after Liver Resection of Hepatocellular Carcinoma a Multicenter Study of 1,324 Patients

Jiong-Jie YU[1], Zhen-Li LI[1], Lei LIANG[1], Jun HAN[1], Hao XING[1], Wan-Guang ZHANG[2], Xian-Hai MAO[3], Yong-Yi ZENG[4], Ting-Hao CHEN[5], Ya-Hao ZHOU[6], Hong WANG[7], Timothy M. PAWLIK[8], Han WU[1], Wan Yee LAU[1,9], Han ZHANG[1], Chao LI[1], Feng SHEN[1], Tian YANG[1]

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Aims: Mortality following liver resection has decreased dramatically over the last several decades such that some centers report a zero incidence of mortality. Postoperative morbidity, however, remains a major concern. The aim of this study was to investigate the association between preoperative body mass index (BMI) and postoperative morbidity after liver resection for hepatocellular carcinoma (HCC).

Methods: Consecutive patients who underwent curative-intent liver resection for HCC from 2010 to 2016 in seven Chinese centers were enrolled. Patients were divided into three groups according to preoperative BMI: low-BMI (≤18.4 kg/m^2), normal-BMI (18.5~24.9 kg/m^2) and high-BMI (≥25.0 kg/m^2). Baseline patient characteristics, operative variables, postoperative 30-day mortality and morbidity were compared. Univariable and multivariable analyses were performed to identify independent risk factors associated with postoperative morbidity.

Results: Among 1,324 patients, 108 (8.2%), 733 (55.4%), and 483 (36.5%) were low-BMI, normal-BMI, and high-BMI, respectively. There were no differences in postoperative 30-day mortality among patients based on BMI (P = 0.199). Postoperative 30-day morbidity was, however, higher in low-BMI and high-BMI patients versus patients with a normal-BMI (33.3% and 32.1% vs. 22.9%, P = 0.018 and P < 0.001, respectively). On multivariable analysis low-BMI and high-BMI remained independently associated with increased postoperative morbidity (OR:1.713, 95% CI:1.070-2.743, P = 0.025, and OR:1.534, 95% CI:1.164-2.021, P = 0.002, respectively). Similar results were also noted in the incidence of postoperative 30-day surgical site infection (SSI).

Conclusions: Compared with normal-BMI patients, low-BMI and high-BMI patients had higher postoperative morbidity, as well as a higher incidence of SSI after liver resection for HCC.

PE-200

Effect of Metformin on IGF-R-Induced Apoptosis and Proliferation in Liver Cancer Cells

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Aims: Metformin has been well known to have antineoplastic activity in hepatocellular carcinoma (HCC) cells. Studies on AMPK-related studies and cell cycle inhibition have been reported as HCC inhibitory mechanisms of metformin. This study was performed to determine whether metformin inhibits survival of HCC cells through insulin-like growth factor-1 receptor (IGF-1R) pathway.

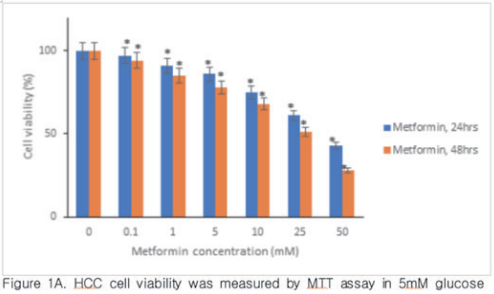

Figure 1A. HCC cell viability was measured by MTT assay in 5mM glucose

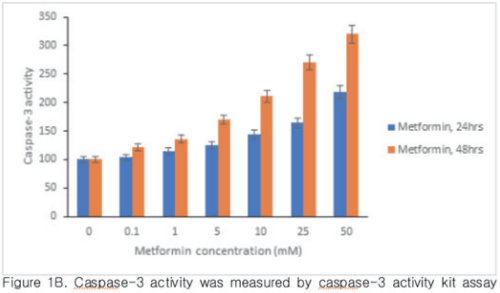

Figure 1B. Caspase-3 activity was measured by caspase-3 activity kit assay in 5mM glucose

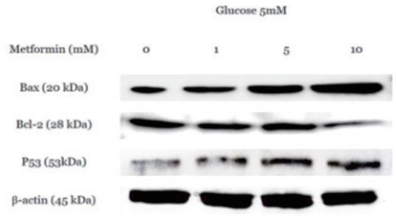

Figure 1C. Check the molecules of apoptosis by Western blot

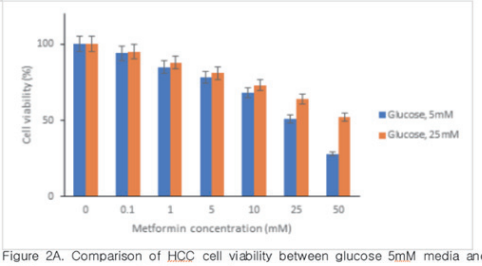

Figure 2A. Comparison of HCC cell viability between glucose 5mM media and 25mM media (Cell viability was measured by MTT assay)

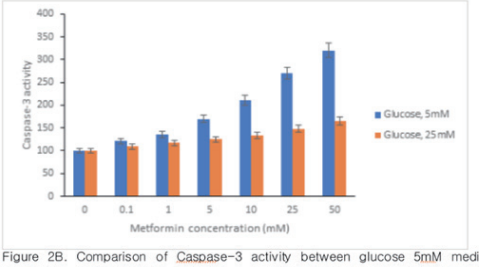

Figure 2B. Comparison of Caspase-3 activity between glucose 5mM media and 25mM media (Caspase-3 activity was measured by caspase-3 activity kit assay)

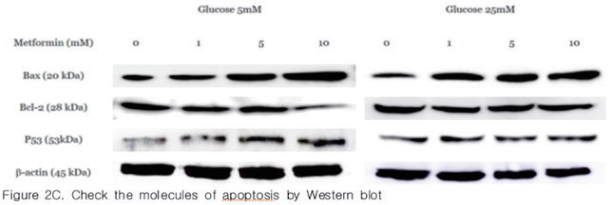

Figure 2C. Check the molecules of apoptosis by Western blot

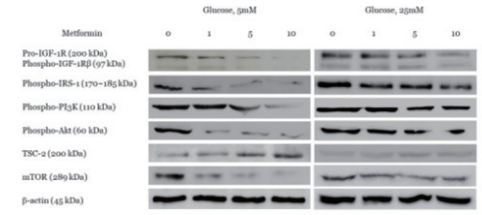

Figure 3A. Check IGF-1R pathway in 5mM and 25mM glucose by Western blot

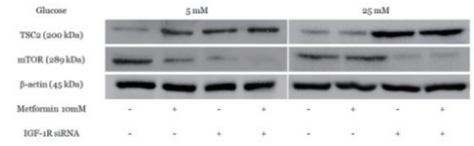

Figure 3B. Check IGF-1R siRNA in 5mM and 25mM glucose by Western blot

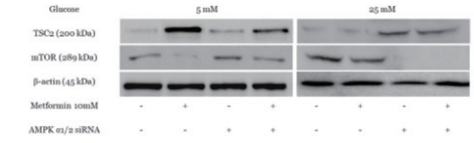

Figure 3C. Check AMPK siRNA in 5mM and 25mM glucose by Western blot

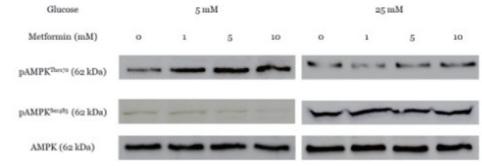

Figure 3D. Check $AMPK^{Thr172}$ phosphorylation and $AMPK^{Ser485}$ phosphorylation in 5mM and 25mM glucose by Western blot

Methods: HCC cell line HepG2 cells were cultured. In order to investigate the effect of metformin on HepG2 cells according to glucose level, cells were cultured in 5mM glucose and 25mM glucose medium. 3-(4, 5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays were performed to determine the effect of metformin on the cell proliferation. Apoptosis was measured by a cell death detection enzyme-linked immunosorbent assay and a caspase-3 activity assay. Expression levels of various proteins, with or without specific small interfering ribonucleic acid-induced gene disruption, were measured by Western blot analysis.

Results: Metformin induces apoptosis of HepG2 cells and reduces cell viability. However, the efficacy of metformin-induced apoptosis was reduced in the hyperglycemic environment (25mM glucose). Metformin reduced IGF-1R activity in HCC cells and decreased IRS-1, PI3K, and Akt activities in IGF-1R pathway, leading to increased TSC-2 activity and decreased mTOR activity. When AMPK siRNA was also used to block AMPK function, metformin caused HepG2 cell apoptosis. In addition, in the normal environment, metformin increased AMPK Thr 172 activity and decreased AMPK Ser 485 activation. However, AMPK Ser 485 activity was increased in hyperglycemic environment as well as AMPK Thr 172.

Conclusions: The inhibitory effect of metformin on HCC cells induces a decrease in IGF-1R activity by metformin and thus pro-

motes apoptosis. In the hyperglycemic environment, the efficacy of metformin on HCC inhibitory effect is decreased, which suggests that the action of mTOR is elevated by AMPK Ser485 phosporylation. Therefore, the use of metformin is helpful in the treatment of liver cancer, especially in hyperglycemia.

Keywords: Metformin, Hepatocellular carcinoma, IGF-1 receptor

PE-201

Liver Cancer Stem Cell Model with Lung Metastasis Developed in the Microenvironment of Hepatocellular Carcinoma

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Aims: Liver cancer considered malignant tumor in or on the liver, which contain different subpopulations, the root of these different subpopulations called cancer stem cells (CSCs). Liver CSCs have been regarded as the cells with specific stem cell-like features in the liver cancer tissue which responsible for tumor initiation growth, progression and metastasis. Lung metastasis considered the most extra-hepatic metastasis of liver cancer. Our group tried to prove the critical role of liver CSC in tumor initiation, and the metastatic Potential responsibility.

Methods: Mouse iPSCs cells were converted for 4 week to liver CSC-like cells in the presence of 50% Huh7cm. The medium was changed every day with fresh medium. The survived cells ($5x10^5$ cells) were injected into the liver of BALB/c nude mice. After 4 weeks malignant tumor was existed in the liver. During the operation, we detected metastatic nodules on the lung. We removed metastatic nodule and the primary tumor. Histopathologic examination and primary culture done for the primary tumor as well as the metastatic nodule. Expression of stem cell markers (Nanog, Oct3/4, Sox2, and Klf4) and CSC markers (CD44, CD90 and ALDH1) were confirmed by rt-qPCR in both the miPS-Huh7cm cells, miPS-Huh7cmP cells and Lung Metastatic nodule (LMN cells). Also, we compared the expression of mechanical marker (fibronectin, vimentin and N-Cadherin) and epithelial marker (E-Cadherin).

Results: We observed that the primary cells from the malignant tumor are rich in CSCs with high expression and expression of metastatic marker compared to converted and LMN cells. These results give us information about the metastatic potential of primary tumor cells which inter to circulation then metastatic to lung.

Conclusions: miPS-Huh7cm cells considered as CSCs with metastatic potential *in vivo*. This model will be very important to understand the molecular mechanisms of metastasis

Keywords: Cancer stem cells, Cancer research, Liver cancer

Liver Cancer, Clinical

PE-202

Association between the Korean National Cancer Screening Program and Liver Cancer-Related Death

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Aims: Little is known about the association between the Korean National Cancer Screening Program (KNCSP) for liver cancer and the cancer-related death. This study aimed to investigate whether nationwide screening by abdominal ultrasonography (US) and alpha-fetoprotein testing is associated with decreased liver cancer-related death of population at risk.

Methods: We hypothesized that improving cancer screening rate might be associated with increasing incidence of liver cancer, but decreasing cancer-related death in the high-risk population. This study collected liver cancer and mortality data between 2008 and 2015 from the national death certificate database of Korea. Information on liver cancer screening of KNSCP was obtained from National Health Screening Statistical Yearbook. Crude death rate and crude incidence rate were obtained and compared. The Joinpoint Regression Program was used to calculate annual percentage change (APC).

Results: The number of patients receiving screening for liver cancer under KNSCP increased from 227,131 to 433,686 between 2008 and 2015. The annual rate of patients on screening per 100,000 persons was 37 in 2008 and 56 in 2015, showing 50.6% of increase (APC, 5.3%; 95% confidence interval [CI], 2.8% to 7.8%). The number of liver cancer-related death decreased from 9,983 to 9,362 (6.2%) during the study period. Crude death rate from liver cancer decreased 21.6% from 48 in 2008 to 38 in 2015 per 100,000 persons (APC, -3.3%; 95% CI, -3.9% to -2.7%). Crude incidence rate decreased 18.8% from 68 in 2008 to 55 in 2015 per 100,000 persons (APC, -2.9%; 95% CI, -3.5% to –2.4%).

Conclusions: Although a certain tendency between KNCSP and liver cancer-related death was observed, the study found little association between them in the given dataset. It's challenging to conclude that the liver cancer-related death decreased by nationwide screening since the incidence rate itself decreased

as well. Future studies considering other aspects that may influence the effectiveness of screening should follow.
Keywords: Screening, Liver cancer, Death

PE-203

Cytochrome P450 4A11 Expression in Tumor Cells: A Favorable Prognostic Factor for Hepatocellular Carcinoma Patients

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Aims: Elevated cytochrome p450 (CYP) 4A gene expression has been linked to the aggravation of various cancers and affects various regulated metabolites. In hepatocellular carcinoma (HCC), the clinicopathological value of CYP4A has not yet been explored, although CYP4A is expressed at high levels in the liver. The goal of this study was to evaluate the clinicopathological value of CYP4A11 expression in HCC.
Methods: We performed immunohistochemical analysis of CYP4A11 and correlated the results with clinicopathological features of HCC (n = 155). Western blotting and reverse transcription–polymerase chain reaction against CYP4A11 and CYP4A22 were also performed for 15 and 20 pairs of fresh-frozen primary HCC and non-neoplastic liver tissue, respectively. Moreover, we analyzed the underlying mechanism by comparing the high and low CYP4A11 mRNA expression groups using gene set enrichment analysis.
Results: CYP4A11 expression level was higher in non-neoplastic hepatocytes than those in HCC cells ($P < 0.001$), and CYP4A11 expression positively correlated with favorable prognostic factors, including tumor size, histological grade, and pathological tumor stage ($P = 0.007$, $P = 0.005$, and $P = 0.007$). Multivariate analysis revealed that CYP4A11 expression was an independent prognostic factor of overall and disease-free survival ($P = 0.002$ and $P = 0.033$). Based on gene set enrichment analysis, high CYP4A11 mRNA expression negatively correlated with the expression of cell cycle-related genes.
Conclusions: These findings support the notion that CYP4A11 expression is a favorable prognostic factor of HCC and suggest potential predictive diagnostic and prognostic roles of CYP4A11 expression in HCC.
Keywords: Cytochrome P450 CYP4A11, Diagnosis, Hepatocellular carcinoma, Prognosis

PE-204

Profiling Cytochrome P450 Family 4 Gene Expression in Human Hepatocellular Carcinoma

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Aims: Cytochrome P450 family 4 (CYP4) enzymes are known as microsomal omega (ω)hydroxylases that metabolize fatty acids, eicosanoids, vitamin D and carcinogens. Thus, CYP4 enzymes may influence tumor development and progression. The aim of the present study was to evaluate the CYP4 expression profile in hepatocellular carcinoma (HCC) and its clinical relevance.
Methods: The present study obtained CYP4 mRNA expression data for 377 HCC cases from The Cancer Genome Atlas cohort and performed Kaplan Meier survival, Gene Ontology functional enrichment, and gene set enrichment analysis (GSEA). In addition, the level of CYP4F2 protein expression was evaluated in matched pairs of HCC and non tumor tissue samples and the results were correlated with the clinicopathological characteristics of HCC (n = 113).
Results: HCC survival analyses indicated better overall survival in patients with high CYP4F2, CYP4F12 and CYP4V2 mRNA expression levels; the results for histologic grade and Tumor-Node-Metastasis stage supported these data. GSEA revealed high levels of CYP4F2, CYP4F12 and CYP4V2 mRNA expression to be negatively correlated with expression of cell cycle-related genes. CYP4F2 protein expression was higher in non-neoplastic liver tissue than in HCC tissue and positively correlated with favorable pathological tumor stage (I versus II-IV) ($P = 0.022$) and was a good independent prognostic factor for overall survival ($P = 0.004$).
Conclusions: These findings demonstrate that the expression levels of genes CYP4F2, CYP4F12 and CYPV2 are favorable prognostic factors in HCC and suggest the potential predictive diagnostic and prognostic roles of CYP4F2, CYP4F12 and CYPV2 gene expression in HCC.
Keywords: Cytochrome P450 family 4, Hepatocellular carcinoma, Diagnosis, Prognosis

PE-205

Quantified Hepatic Stiffness by MR Elastography Is a Marker for Early Recurrence in Patients with HCC within the Milan Criteria

Hyo Jung Cho[1], Bo Hyun Kim[2], Hye Jin Kim[2], Jimi Huh[2], Jai Keun Kim[2], Jei Hee Lee[2], Chul Won Seo[1,3], Young-hwan Ahn[1], Jinhee Jung[1], Jung Woo Eun[1], Soon Sun Kim[1], Sung Won Cho[1], and Jae Youn Cheong[1]

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Aims: Magnetic Resonance Elastography (MRE) is a non-invasive tool for measuring hepatic stiffness (HS) with high diagnostic accuracy. In this study, we tried to investigate whether quantified HS by MRE could predict the prognosis of patients with hepatocellular carcinoma (HCC) within the Milan criteria.

Methods: This study was designed as a retrospective study. The HCC patients within Milan criteria with available pre-treatment quantified HS by MRE were reviewed and those who achieved complete remission (CR) after hepatic resection, radiofrequency ablation, or trans-arterial chemoembolization were included. Cox regression and Kaplan-Meier analyses were performed to identify risk factors associated with recurrence or survival.

Results: A total of 110 HCC patients who underwent hepatic resection (n = 75), RFA (n = 11) or TACE (n = 24) were included. Higher liver stiffness (> 4.5 kPa; (hazard ratio [HR] = 3.65; 95% confidence interval [CI] = 1.63–8.18; *P* = 0.002) was identified as an independent risk factor for predicting early HCC recurrence. In the subgroup analysis for patients who underwent curative treatment (including hepatic resection and RFA), higher HS was also identified as an independent risk factor for predicting early HCC recurrence (HR = 5.95; 95% CI = 2.14-16.53; *P* = 0.001). There was no significant variable associated with liver transplantation-free-survival.

Conclusions: Pre-treatment HS measured by MRE is a potential biomarker for predicting early tumor recurrence in the patients with HCC within the Milan criteria after CR.

Keywords: Magnetic resonance elastography, Hepatocellular carcinoma, Hepatic stiffness, Recurrence

PE-206

Antiviral Treatment Status at Hepatocellular Carcinoma Development Affects Overall Survival in Chronic Hepatitis B Patients

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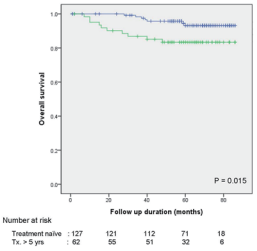
Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Despite potent antiviral therapy for hepatitis B virus (HBV), some patients still develop hepatocellular carcinoma (HCC). Whether characteristics and prognosis of HCCs developed in such patients differ from those developed in antiviral treatment-naïve patients is unknown. We aimed to compare the prognosis of patients who developed HBV-related HCC while on long-term antiviral therapy and those who developed HBV-related HCC while treatment-naïve.

Methods: A total of 189 patients (127 without antiviral treatment history and 62 with more than 5 years of antiviral treatment history) diagnosed with modified UICC stage I HBV-related HCC between 2011 and 2013 were analyzed.

Results: During a median 5 years of follow-up, mortality was observed in 17 patients (9%). The overall survival was better in treatment-naïve patients compared to patients who have received antiviral therapy for more than 5 years (5-year overall survival rates: 93.2% vs 83.3%, respectively, *P* = 0.015). There was no significant difference in recurrence free survival between two groups (5-year recurrence free survival rates: 59.3% vs 61.8%, respectively, *P* = 0.612). In contrast, ALBI score at 12 months after HCC diagnosis improved in treatment-naïve patients (-0.03 ± 0.37) while it aggravated in patients who have been under antiviral therapy for 5 years or more (0.10 ± 0.26) (*P* = 0.006). Liver failure without HCC progression as a cause of morality was observed only in patients who have received antiviral therapy for more than 5 years (4 of 10 patients, 40% vs. 0%).



	Treatment naïve (n=127)	Treatment > 5 years (n=62)	p-value
Δ ALBI score			
6 months	0.013 ± 0.38	0.127 ± 0.21	0.012
12 months	- 0.031 ± 0.37	0.100 ± 0.26	0.006

Conclusions: Worse survival in patients who develop HBV-related HCC after long-term antiviral therapy can be attributed to less potential for liver function improvement compared to those who develop HCC while treatment-naïve. More attention should be given to changes in liver function when treating patients who develop HCC despite long term antiviral therapy.

Keywords: Hepatocellular carcinoma, Antiviral treatment status, Overall survival, Liver function

PE-207

Hepatitis C Virus Genotype Affects the Survival of Patients with Hepatocellular Carcinoma

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sang National University Changwon Hospital, Changwon, Republic of Korea; [3]Institute of Health Sciences, Gyeongsang National University, Jinju, Republic of Korea

Aims: There is no current evidence that hepatitis C virus (HCV) genotypes will have a worse effect on the survival of patients with hepatocellular carcinoma (HCC). This study aimed to investigate whether the HCV genotype could affect the survival rate of patients with HCV-related HCC.
Methods: We performed a retrospective cohort study using the data of patients with HCV-related HCC evaluated at 2 centers in Korea between January 2005 and December 2016. Propensity score matching between genotype 2 and non-genotype 2 was performed to reduce bias.
Results: A total of 180 patients were enrolled. Of these, 86, 78, and 16 had genotype 1, genotype 2, and genotype 3 HCV infections, respectively. The median age was 66.0 years, and the median overall survival was 28.6 months. In the overall cohort, patients with genotype 2 (31.7 months) had longer median overall survival than patients with genotype 1 (28.7 months; P = 0.004) and genotype 3 (15.0 months; P = 0.003). In the propensity score–matched cohort, patients with genotype 2 also showed a better survival rate than patients with non-genotype 2 (P = 0.007). Patients with genotype 2 had a longer median decompensation-free survival than those with non-genotype 2 (P = 0.001). However, there was no significant difference in recurrence-free survival in patients who underwent curative treatment between genotype 2 and non-genotype 2 (P = 0.077). In multivariate Cox regression analysis, non-genotype 2 (hazard ratio, 2.19; 95% confidence interval, 1.29-3.71) remained an independent risk factor for death.
Conclusions: Among patients with HCV-related HCC, those with genotype 2 have better survival.
Keywords: Hepatocellular carcinoma, Survival, Genotype, Hepatitis C virus

PE-208

Factors Associated with Postprogression Survival in Advanced Hepatocellular Carcinoma Patients with Post-Sorafenib Progression Not Eligible for Regorafenib

Hee Yeon Kim[1,2], Chang Wook Kim[1,2], Sang Wook Choi[1,2], Do Seon Song[1,2], U Im Chang[1,2], Jin Mo Yang[1,2], Sung Won Lee[1,2], Hae Lim Lee[1,2], Nam Ik Han[1,2], Sun Hong Yoo[1,2], Jung Hyun Kwon[1,2], Soon Woo Nam[1,2], Pil Soo Sung[1,2], Jeong Won Jang[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

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Aims: We aimed to investigate the prognostic factors associated with postprogression survival (PPS) in advanced hepatocellular carcinoma (HCC) patients who showed radiological progressive disease (PD) following sorafenib monotherapy, and were not eligible for 2nd-line regorafenib treatment.
Methods: Total of 223 patients who were confirmed with radiological PD following sorafenib monotherapy from September 2008 to December 2017 were enrolled. We define those with Child-Pugh class A, ECOG PS 0 or 1 at progression, and who had tolerated sorafenib as candidates eligible for 2nd line regorafenib therapy.
Results: Among 223 patients with PD after sorafenib treatment, 126 (56.5%) patients met eligibility criteria for regorafenib treatment at first radiological confirmation of PD. The median PPS of the candidates for regorafenib treatment (12.1 months) was statistically longer (P < 0.001) than that of the non-candidates (3.2 months). Prognostic factor associated with good PPS in non-candidates for regorafenib therapy was absence of macrovascular invasion [hazard ratio = 0.5 (95% confidence interval 0.33-0.76)] at initial radiological PD.
Conclusions: Absence of macrovascular invasion at initial radiological PD following sorafenib may predict good PPS in advanced HCC patients who had progressed after sorafenib monoterapy and were not eligible for 2nd-line regorafenib treatment.
Keywords: Prognosis, Hepatocellular carcinoma, Sorafenib, Progression

PE-209

Diagnostic Value of Protein Induced by Vitamin K Absence in Hepatocellular Carcinoma Patients with Normal Alpha-Fetoprotein Level

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Aims: The aim of this study was the evaluation of the changes of protein induced by vitamin K absence (PIVKA-II) levels in hepatocellular carcinoma patients having normal Alpha-fetoprotein(AFP) levels.
Methods: A total of 83 patients diagnosed of hepatocellular carcinoma (HCC) based on histopathlogy with the normal level of AFP (≤ 20ng/mL) were tested by PIVKA-II (a cut-off value of 40 mAU/ml), and then classified the stage of liver cancer based on size, number of tumors, Child-Pugh score, vascular invasion and BCLC classification.
Results: A total 83 patients were enrolled and performed *liver biopsy* for the *diagnosis* of HCC. The average age of patients was 58 ± 9.6 years and the 69 patients (83.1%) were men. The mainly cause of HCC was HBV infection in 68 patients (81.9%), in BCLC stages A, B, C and D of 43.4%, 37.4%, 13.3%, and 6%, respectively. All patients having the normal AFP level, the proportion of patients with concentration of PIVKA-II increased to 73.4%, the mean level of PIVKA-II was 4693.7±10017.1. Serum PIVKA-II levels significantly increased according to BCLC stage (P = 0.002) and correlated with tumor size (P = 0.001),

the PIVKA-II level was significantly higher in the vascular invasive group than in the non vascular invasive group ($P = 0.03$).
Conclusions: PIVKA-II was a maker that could improve the diagnostic of hepatocellular carcinoma in patients with normal AFP value.
Keywords: PIVKA-II, Hepatocellular carcinoma, AFP, Live cancer

PE-210

Comparing Characteristics, Treatment Outcomes of Non-B Non-C Virus and Hepatitis Virus-Related Hepatocellular Carcinoma

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Aims: To compare the clinical characteristics, treatment outcomes of hepatocellular carcinoma (HCC) due to viral B, C hepatitis and non-B, non-C patients.
Methods: This prospective study involved 118 patients divided into the viral HCC group (76 patients) and non B,C HCC (NBC-HCC) group (42 patients). All patients were underwent one session of transarterial chemoembolization (TACE) procedure. Two groups of patients were compared in rate of baseline characteristics. An AFP response was defined as a decrease in AFP at least 50% after treatment. Imaging response was evaluated according to the modified Response Evaluation Criteria in Solid Tumours (mRECIST).
Results: The differences of the age, gender, Child-Pugh score, BCLC score, tumor location, number of tumor, size of tumor, branch portal vein thrombosis before treatment between the viral-HCC group and NBC-HCC group were not statistically significant ($P > 0.05$ for all). Changes in mean of size of the tumor and AFP level both group after treatment were significant, $P < 0.05$. Comparing achievement of stagnant arterial flow, in viral-HCC group rate of complete occlusion was 61.8%, in NBC-HCC group was 59.5%, $P = 0.6$. 40.8% patients with AFP response were identified in viral-HCC group, this rate in NBC-HCC group was 71.4%, $P = 0.001$. Tumor response rate in viral-HCC was not significantly different from NBC-HCC (72.4% and 78.6%, $P = 0.6$).
Conclusions: NBC-HCC patients presented same clinical characteristics as compared with viral HCC. Despite this state, NBC-HCC patients had better outcome in AFP response than virus-related HCC.
Keywords: Hepatocellular carcinoma, Viral hepatitis, Transarterial chemoembolization

PE-211

Lenvatinib Is Independently Associated with the Reduced Risk of Progressive Disease When Compared to Sorafenib in Patients with Hepatocellular Carcinoma

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Aims: Treatment outcome of lenvatinib is not inferior to that of sorafenib in treating patients with unresectable hepatocellular carcinoma (HCC). We compared treatment outcomes of lenvatinib and sorafenib and identified independent predictors of progressive disease (PD) at early time-point in patients with unresectable HCC.
Methods: Patients with unresectable HCC treated with lenvatinib (n = 10, 26.3%) or sorafenib (n = 28, 73.7%) between October 2018 and December 2019 were retrospectively recruited. The treatment response was assessed using the modified RECIST criteria.
Results: Patients treated with lenvatinib were likely to have ECOG 1 (vs. 0) performance (30.0% vs. 10.7%), larger maximal tumor size (mean 6.9 vs. 3.3 cm), and less macroscopic portal vein invasion (80.0% vs. 32.1%) than those treated with sorafenib (all $P < 0.05$). During the follow-up (median 2.0 months), 17 (44.7%) patients experienced PD. The proportion of Child-Pugh class B (vs. A) and multiple tumors were significantly higher in patients treated with lenvatinib than those treated with lenvatinib (all $P < 0.05$). On multivariate analysis, lenvatinib was independently associated with the reduced risk of PD (odds ratio=0.098, 95% confidence interval, 0.010–0.952, $P = 0.045$), whereas multiple tumor was independently associated with the increased risk of PD (odds ratio=14.665, 95% CI, 1.670–128.787, $P = 0.015$). The progression-free survival tended to be longer in patients treated with lenvatinib than those treated with sorafenib (4.1 vs. 2.0 months, $P = 0.059$ by log-rank test).
Conclusions: Lenvatinib was better is progression-free survival than sorafenib in unresectable HCC. Large-scale study is required for validation in Korean cohort.
Keywords: Hepatocellular carcinoma, Lenvatinib, Sorafenib

PE-212

Substantial Risk of Hepatocellular Carcinoma Recurrence Even after Five Years of No-Recurrence Period among Early Stage Hepatocellular Carcinoma Patients Treated with Resection or Radiofrequency Ablation

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Aims: Although hepatocellular carcinoma (HCC) is notorious for its high recurrence rate, some patients do not experience recurrence for more than five years after resection or radiofrequency ablation for early stage HCC. Incidence and risk factors for HCC recurrence after five years of no-recurrence period remain

unknown. The aim of this study was to identify the risk and risk factors of recurrence among patients who did not experience recurrence for long period.

Methods: A total of 1451 consecutive patients (median: 55 years old, male: 79.0%, hepatitis B virus: 76.7%) with good liver function (Child Pugh class A) who were diagnosed with early stage HCC, and received radiofrequency ablation or resection as initial treatment between 2005 and 2010 were analyzed. Among them, 477 patients were alive and without recurrence at 5-years.

Results: During a median follow-up period of 8.1 years, 961 patients (66.2%) experienced HCC recurrence. The cumulative recurrence rates at 2-year and 5-year were 39.2% and 57.8%, respectively. Of the 477 patients who were alive and without recurrence at 5-years, 122 patients (25.5%) experienced recurrence. For them, the next 5-year cumulative recurrence rate was 30%. While sex, albumin-bilirubin grade, alphafetoprotein (AFP) level, tumor number, maximal tumor diameter and treatment modality at diagnosis were associated with early recurrence (within 2 years), sex, fibrosis-4 (FIB-4) score, and AFP levels were associated with further HCC recurrence among patients who did not experience recurrence for more than five years.

Conclusions: HCC recurrence rate was substantially high even after five years of no-recurrence period after HCC treatment. HCC patients warrant continued HCC surveillance even after five years of no-recurrence period, especially for men, high FIB-4 score, and elevated AFP levels at 5-years.

Keywords: Hepatocellular carcinoma, Recurrence, Early stage, No-recurrence period

PE-213

Indications for Endoscopic Screening and Prophylaxis of Esophageal Varices in Patients with Hepatocellular Carcinoma Invading Portal Vein

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Aims: Given the short life expectancy of patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) probably yielding increased portal pressure, we aimed to identify risk factors for high-risk esophageal varices and potential predictors for variceal bleeding, in order to determine indications for variceal screening and prophylaxis in such patients.

Methods: This study included 255 asymptomatic patients with HCC-PVTT registered in a hospital-based cancer registry of Asan Medical Center. All patients experienced upper endoscopy for variceal screening and had no prior history of variceal hemorrhage or endoscopic prophylaxis. We examined clinico-endoscopic risk factors of high-risk varices, defined as large/medium varices or small varices with red-color sign, in the entire patients, and subsequently, significant predictors for variceal hemorrhage in a subset of 106 patients with any grade of varices.

Results: Of the 255 patients screened by endoscopy, 60 (23.5%) had high-risk varices; and 149 (66.2%) did not have varices, with 31 (12.2%) having solitary or combined gastric varices. Most of patients had Child-Pugh class A liver function; one-third did infiltrative tumors; and one-fifth did metastatic lesions. In terms of patterns of PVTT, ≥Vp2, Vp3, and Vp4 disease existed in 87 (34.1%), 65 (25.5%), and 103 (40.4%) respectively. As initial therapy for HCC, chemoembolization (67.5%) was most common, and radiotherapy for PVTT was done in 32.5% of the patients. Vp4 grade and low platelet count were independently correlated with high-risk varices. A total of 18 bleeders (7.1%) with 11 high-risk (18.3%) and 7 low-risk (3.6%) varices occurred during the median follow-up of 13.8 months. Multivariate Cox analysis revealed that infiltrative HCC and red-color sign on varices were significant predictors of variceal bleeding over time, as were not beta-blockers, radiotherapy, sorafenib treatment and the degrees of Vp, coagulopathy and hepatic function. Neither high-risk varices nor variceal bleeding did not affect survival of patients (log-rank test, $P = 0.179$ and $P = 0.867$, respectively). ≥Vp2: segmental branches of portal vein or above, Vp3: lobe large branches of portal vein, Vp4: the main trunk of portal vein or superior mesenteric vein or inferior vein cava.

Conclusions: Our data indicate that variceal screening should be considered in patients with HCC-PVTT extending to the major PVTT, and prophylactic variceal ligation may be needed in selected patients.

Keywords: Esophageal varix, Variceal bleeding, Hepatocellular carcinoma, Portal vein tumor thrombus

PE-214

Alpha-Fetoprotein L3 Level, Not an L3 Fraction, Is an Useful Marker for the Diagnosis of Hepatocellular Carcinoma

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Aims: Though serum lens culinaris agglutinin-reactive fraction of α-fetoprotein (AFP-L3) level has been proposed as a potential diagnostic marker of hepatocellular carcinoma (HCC), it is still controversial whether AFP-L3 level has higher accuracy than other markers.

Methods: Total 411 patients who underwent AFP and AFP-L3 tests were included. AFP-L3 level was estimated with the following formula: AFP-L3 level (ng/mL) = serum AFP level (ng/mL) × L3 fraction (%).

Results: Among total 411 patients, 150 (36.5%) patients had no underlying liver disease, 150 (36.5%) patients had chronic liver disease without HCC, and 111 (27.0%) patients had HCC. Except for patients with no underlying liver disease, chronic hepatitis B was the most common underlying liver disease (155 patients, 37.7%). All patients had imaging test, 66 (16.1%) patients had no space-occupying lesion (SOL), 111 (27.0%) patients had HCC, 20 (4.9%) had dysplastic nodule, 214 (52.0%) patients had benign nodules. The area under the receiver operating characteristics curve (AUROCs) of AFP-L3 level, AFP level, and AFP-L3 fraction were 0.812 (95% confidence interval [CI], 0.771-0.848), 0.768 (95% CI, 0.724-0.808) and 0.797 (95% CI, 0.755-0.835). AUROCs of AFP-L3 level were significantly higher than AFP level for the diagnosis of HCC ($P < 0.001$). There were no significant differences between the AUROCs of AFP level and AFP-L3 fraction ($P = 0.1645$), and those of AFP-L3 level and AFP-L3 fraction ($P = 0.2886$). With the cut-off value of 5.1 ng/mL, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of AFP level were 73.0%, 65.7%, 44.0% and 86.8%. While, with the cut-off value of 2.5 ng/mL, the sensitivity, specificity, PPV and NPV of AFP-L3 level were 72.1%, 80.3%, 57.6% and 88.6%.

Conclusions: AFP-L3 level, rather than L3 fraction, is more useful marker for the diagnosis of HCC than serum AFP level.

Keywords: Lens culinaris agglutinin-reactive fraction of α-fetoprotein, Hepatocellular carcinoma, Tumor marker

PE-215

Clinical Manifestations and Prognosis of Non-Cirrhotic and Cirrhotic Hepatocellular Carcinoma Patients with Chronic Hepatitis B

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Aims: The differences of the clinical features and survival outcomes between cirrhotic and non-cirrhotic HCC patients with hepatitis B virus (HBV) infection remain to be determined. We evaluated clinical characteristics and prognosis of non-cirrhotic HBV-associated HCC patients compared with cirrhotic patients.

Methods: Between January 2005 and December 2015, 1,345 patients were diagnosed to have HCC at our hospital. Of these, 860 HBV-associated HCC patients with (cirrhotic group, n = 519, 60.3%) or without cirrhosis (non-cirrhotic group, n = 341, 39.7%) were retrospectively analyzed. Propensity score matching (PSM) was used to adjust for differences between the two groups.

Results: The non-cirrhotic group had lower Child-Turcotte-Pugh (CTP) classes, greater tumor sizes, and were less likely to have portal vein thrombosis than the cirrhotic group. Age and gender were not significant different between the two groups. Cumulative overall survival (OS) rates at 2, 4, 6, and 8 years after treatment were significantly higher in the non-cirrhotic group (67.2%, 57.1%, 43.2%, and 38.3% *vs.* 58.3%, 41.3%, 33.2%, and 27.8%, respectively, p-value < 0.001). However, no significant intergroup difference in OS rates was observed after PSM (p-value = 0.680). Significant predictive factors of OS were CTP class, tumor size, tumor number, and curative-intended treatment for the cirrhotic group.

Conclusions: After PSM, cumulative OS rates were no difference between HBV-related HCC patients with and without cirrhosis, and they were clearly dependent on CTP class, regardless of the presence of cirrhosis itself both in in cirrhotic and non-cirrhotic patients.

Keywords: Hepatitis B, Cirrhosis, Hepatocellular carcinoma

PE-216

Albumin-Bilirubin Grade Can Subclassify Patients with a Child-Pugh Score of 5 Treated with Sorafenib for Hepatocellular Carcinoma

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Aims: The Albumin-Bilirubin (ALBI) grade is a recently developed index to assess hepatic reserve and prognosis in patients with hepatocellular carcinoma (HCC). We aimed to investigate the prognostic value of ALBI grade in advanced HCC patients who received sorafenib.

Methods: From September 2008 to October 2017, a total of 786 consecutive patients with advanced HCC who received sorafenib monotherapy were retrospectively included from six University hospitals in Korea. Serum albumin and bilirubin values were used to determine ALBI grade. Overall survival was stratified by ALBI grade using the Kaplan-Meier method. A Cox proportional hazard model was used to identify independent factors for influencing overall survival.

Results: Hepatitis B virus-related HCCs comprised 75.4% (593/786) of enrolled patients. Among 786 enrolled patients, 161 (20.5%), 555 (70.6%), and 70 (8.9%) were classified as ALBI grade 1, 2, and 3, respectively, in baseline. Majority of the patients with ALBI grade 1 (150/161, 93.1%) had a Child-Pugh score of 5. Among patients with ALBI grade 2, 30.9% (172 patients) had a Child-Pugh score of 5 and 52.3% (290 patients) had a Child-Pugh score of 6. The median OS was 16.5, 10.1, and 7.4 months for ALBI grade 1, 2, and 3, respectively ($P < 0.001$). Cox regression analysis showed that baseline ALBI grade strongly influenced the mortality of HCC patients receiving sorafenib. Among patients with a Child-Pugh score of 5, overall survival was significantly different between patients with

ALBI grades 1 and 2. However, there were no significant differences in overall survival between patients with ALBI grades 1 and 2 among patients with a Child-Pugh score of 6.
Conclusions: The ALBI grade is of significant prognostic importance in subclassifying patients with a Child-Pugh score of 5 who received sorafenib for HCC.
Keywords: Albumin-bilirubin grade, Hepatocellular carcinoma, Sorafenib, Prognosis

PE-217

Differentiation between Hepatocellular Carcinoma and Other Hepatic Malignancy in Cirrhosis: Performance of LI-RADS 2018

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Aims: To evaluate the diagnostic accuracy of Liver Imaging Reporting and Data System (LI-RADS) v2018 for differentiating between hepatocellular carcinoma (HCC) and other hepatic malignancy (OM) in patients with liver cirrhosis.
Methods: From 2008 to 2017, 55 patients with untreated OM and liver cirrhosis were eligible for this retrospective case-control study (mean age, 58 ± 10 years; 45 men and 10 women). Controls consisted of 165 treatment-naïve patients with HCC and liver cirrhosis (mean age, 58 ± 10 years; 134 men and 31 women). Two radiologists blinded to the final diagnosis independently and retrospectively determined the presence of LR-M features and major HCC features (nonrim arterial phase hyperenhancement, nonperipheral washout, and enhancing capsule). The diagnostic performances of each imaging feature, LR-M criteria, and LR-5 criteria were calculated and compared by using the generalized estimating equation method.
Results: Individual LR-M features had sensitivity of 9–71% and specificity of 83–97% for diagnosing OM. Major features of HCC had sensitivity of 62–83% and specificity of 69–89% for diagnosing HCC. The LR-M criteria had sensitivity of 89% (95% confidence interval [CI], 81–97) for diagnosing OM, with specificity of 48% (95% CI, 40–56). The LR-5 criteria had a sensitivity of 74% (95% CI, 67–81) for diagnosing HCC, with a specificity of 89% (95% CI, 81–97). The accuracy of LR-5 criteria was higher than that of LR-M criteria (78% [95% CI, 72–83] vs. 58% [95% CI, 52–65], $P < .001$).
Conclusions: The LR-5 and LR-M criteria provide comparable performances for differentiating between hepatocellular carcinoma and other hepatic malignancy with LI-RADS v2018.
Keywords: Cirrhosis, Diagnosis, Liver cancer, Magnetic resonance imaging

PE-218

Epidemiological and Clinical Features of Patients with HCC in Mongolian and Russian Population

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Aims: Among all oncological diseases, liver cancer is the 3rd in Mongolian and 5th in Russian most common. We sought to describe the clinical and epidemiological characteristics and outcomes of HCC patients from Mongolia and Russia.
Methods: The studies were carried out in the cross-border regions of Mongolia and Asian part of Russia in the Lake Baikal region (Irkutsk region). 349 patients with hepatocellular carcinoma (HCC) of the Caucasian and Mongolia races were enrolled in the study.
Results: HCC incidence (2015) shows more unfavorable trends in the territory of Mongolia (74.5 per 100,000 total population)compared to Asian region of Russia (8.45 per 100,000). Patients from Mongolia often have a history of jaundice and acute hepatitis, HCC patients in Mongolia are related with HBV or HCV in 94.4% and 76.0% in Russia. Out of the etiological factors HCC is more often associated with the hepatitis B virus in Mongolia (34.4%) than in the Asian part of Russia(17.1%). At the same time, in Caucasians, HCC developed primarily on the background of liver cirrhosis.
Conclusions: Mongolia in terms of the incidence of HCC belongs to the hyper endemic regions of the world. In this country, among the risk factors, HBV continues to play a big role. Due to the high incidence and late diagnosis in both countries, there is a need to develop a national strategy for early diagnosis and treatment of patients with HCC.
Keywords: Liver cancer, Epidemiology, Mongolia, HCC

PE-219

Management of Hepatocellular Carcinoma in Mongolia

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Aims: This study will evaluate the efficacy of selective internal

radiation therapy (SIRT) using SIR-Spheres® yttrium-90 resin microspheres compared to sorafenib in the treatment of patients with locally advanced hepatocellular carcinoma (HCC).

Methods: Total 360 patients were enrolled to the study from 27 sites of Asia-Pacific 11 countries. The National Cancer Center of Mongolia was one of the sites this study and we were recruited a total 39 patients into the study from March 2011 to June 2016 in Mongolia. In this multicenter, phase III, randomized-controlled clinic trial, we randomly assigned patients with advanced hepatocellular carcinoma who had not received surgical therapy for HCC to receive sorafenib (at a dose of 400mg twice daily) or yttrium-90 resin microspheres by the transarterial route.

Results: Among the 39 patients recruited in Mongolia, 19 received at least one dose sorafenib and 20 received SIRT treatment in Singapore; these patients were included in the safety analysis. Adverse events that were reported for patients receiving sorafenib were predominantly grade 1 or 2 in gastrointestinal, constitutional and dermatologic in nature. The most frequently reported drug-related adverse events in patients treated with sorafenib were hypertension, hand-foot skin reaction, diarrhea, alopecia, fatigue. Common procedure-related adverse events were usually mild (grade 1/2) and included nausea and vomiting (27.7% all grades) and abdominal pain (22.1% all grades), with very few grade 3.

Conclusions: We found that patients treated SIRT had significantly fewer total numbers of adverse events (p 0.0964) when compared with those treated with sorafenib.

Keywords: HCC, Managment, Mongolia

PE-220

Evaluation of the American Joint Committee on Cancer (AJCC) 8th Edition Staging System for Hepatocellular Carcinoma in 1,034 Patients with Curative Resection

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Aims: Recently, 8th edition staging system of the American Joint Committee on Cancer (AJCC) was released with change in T stage. We validated the prognostic value of the new AJCC staging system in comparison to the previous 7th edition.

Methods: Total 1,034 patients who had undergone curative resection as the initial treatment for hepatocellular carcinoma (HCC) at Samsung Medical Center, Seoul, Korea, between 2008 and 2012, were enrolled in this study. Pathology T stage was determined by AJCC 7th and 8th edition, respectively. Recurrence free survival (RFS) was estimated using the Kaplan-Meier method and compared by log-rank test. The analysis of the time dependent receiver-operating-characteristic (ROC) curves for censored survival data was used to compare the capability of the two models to predict tumor recurrence.

Results: The median follow up period was 64.9 months (range: 0.8-112.5 months). The 1-, 3- and 5-year RFS rates were 77.7%, 61.8% and 56.4%, respectively. Among 477 T1 patients by 7th edition, 157 were re-classified as T1a, and 320 as T1b by 8th edition. Stage migration was observed in 65 patients (6.3%); from T2 to T1a in 45 patients and from T3 to T4 in 20 patients. AJCC 7th edition and 8th edition showed similar predictive ability, and the 2 year AUC value were comparable in 7th and 8th edition (0.693 vs. 0.690). RFS was not different between T1a and T1b by 8th edition (P = 0.256). For solitary tumors ≤2 cm (T1a by 8th edition), those with microvascular invasion (n = 54) had shorter RFS than those without it (n = 171) (P = 0.016), although there is no such distinction in 8th edition. Tumors involving a major branch of portal vein or hepatic vein (T4 by 8th edition and T3b by 7th edition, n = 20) showed shorter RFS than multifocal tumors at least one of which is >5 cm (T3 by 8th edition and T3a by 7th edition, n = 40) (P = 0.017), supporting the change in 8th edition. RFS was comparable between solitary tumors >2 cm with vascular invasion (n = 375) and multifocal tumors ≤5 cm (n = 92), which were classified as a single category T2 in both 7th and 8th editions. For multifocal tumors ≤5 cm, survival showed no difference according to presence of vascular invasion.

Conclusions: The AJCC 8th edition staging system for HCC showed comparable predictive performance to the 7th edition. It is desirable in future revision to consider sub-stratification of solitary tumors ≤2 cm (T1a) depending on the presence of vascular invasion, which is not included in 8th edition. Further studies are required to validate these findings.

Keywords: Hepatocellular carcinom, Prognosis, Stage, AJCC

PE-221

Application of Multimodal Image Fusion Technology in the Diagnosis and Treatment of Intrahepatic Cholangiocarcinoma

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Aims: To explore the value of multimodal image fusion in preoperative planning and intraoperative navigation of intrahepatic cholangiocarcinoma (ICC).

Methods: Clinical data of 11 patients with intrahepatic cholangiocarcinoma who underwent multimodal image fusion technology from January 2018 to September 2018 in the Department of Hepatobiliary, Zhujiang Hospital were retrospectively analyzed. CT enhanced scan and MRI enhanced scan with gadoxetate disodium (Gd-EOB-DTPA) of the upper abdomen were respectively performed, and 3D models of individualized

liver, tumor, and intrahepatic vessel were constructed based on CT-MRI fusion images. The ICG molecular fluorescence imaging system and the augmented reality navigation system were used to guide hepatectomy.

Results: The display of grade 3 and above branch vessels of the portal vein and hepatic vein system by enhanced CT was clearer than that of MRI (100% vs 36.4%, $P = 0.035$); while enhanced MRI showed clearer tumor margin than CT (100% vs 36.4%, $P = 0.004$) (Table 1). Eleven liver cancer lesions were detected by enhanced CT and 13 by enhanced MRI (including 2 lesions not demonstrated by enhanced CT with maximum diameter ≤ 10mm). No blood transfusion was found in 11 patients during perioperative period. No liver failure, bile leakage and death occurred after operation.

Conclusions: Multimodal image fusion technique is helpful to optimize the preoperative surgical plan, which can assist the recognition of important vessels and real-time navigation of hepatectomy during operation, and improve the safety of operation.

PE-222

An Astonishing Familiar Cluster of Intrahepatic Cholangiocarcinoma (ICC) in Wilson's Disease (WD)

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Aims: According to literature, the rate of hepatobiliary malignancies in WD is low; occasional cases of hepatocellular carcinoma (HCC) have been reported with even rarer incidence of ICC. We report the case of a family with WD in which two siblings, Mr F and Mr G, developed ICC at the ages of 56 and 60 respectively while their sister was affected by WD without primary liver malignancies.

Methods: We made a literature search for publications including age at ICC diagnosis, time between diagnosis of WD and tumor detection and type of therapy.

Results: Literature data report up to now only thirteen cases of ICC associated with WD. Nothwithstanding considerable heterogeneity of treatment all the patients who underwent surgical resection were alive after two years. Mr F underwent primary surgery for ICC and he relapsed after one year. The patient, therefore, had liver transplantation in November 2018 after conversion chemotherapy with Gemcitabine - Cisplatin schedule achieving a surprising complete response. Next Generation Sequencing (NGS) found an undescribed FGFR2 oncogenic somatic mutation. Mr G developed ICC and HCC one year later. The two malignancies were treated with surgical resection and the patient is currently without any evidence of recurrence of the disease after four years.

Conclusions: While the reasons for the low incidence of ICC in WD remains obscure, we underline the exceptional findings of two ICC in two siblings in absence of additional definite risk factors, one of which showed complete response to chemotherapy.

PE-223

Serologic Detection of Autoantibodies from Patients with Cholangiocarcinoma by Proteomic Approach

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Aims: Autoantibodies can be used clinically for cancer detection which can be identified by proteomic analysis of tumor associated antigens (TAAs) that are potentially involved in malignant transformation. The purpose of the present study was to detect the autoantibodies in sera of patients with cholangiocarcinoma by serological proteomic approach for early cancer diagnosis.

Methods: Serum samples were obtained from 9 patients with CC and from 5 healthy volunteers. The European Cell Culture Bank provided cholangiocarcinoma cell lines (CCSW1 and CCLP1).Proteins were separated using 2 DE. Then proteins were transferred on to nitrocellulose membrane and proteins were detected using enzyme conjugated secondary antibody and ECL substrate (enhanced chemiluminescent) generated signals were visualized by X-films. Silver staining was used to see the migration pattern on gels.

Results: 2-D electrophoresis maps of CC cell lines shown different protein distributions. After silver staining, an average of 160-180 spots were detected from CCSW1, mainly between pH 4 and 8, with molecular weight ranging from 40 to 90 kDa. With CCLP1, between 80 and 100 spots were distributed in acidic parts of the map with MW from 20 to 90 kDa. By comparative blotting analysis, four common immunoreactive spots were found in CCSW1 blots with and two out of nine CC patient sera but not with control sera, whereas two common immunoreactive spots were found only with control sera. With CCLP1, no common spot observed in immunoblots with CC sera.

Conclusions: The detected immunoreactive protein spots might correspond to the autoantibodies produced to the homologous tumor associated antigens.

PE-224

Predictive Factors and Treatment Outcome for Recurrent Intra-Hepatic Cholangicarcinoma

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Aims: Intrahepatic cholangiocarcinoma (ICC) had devastating outcome owing to advanced stage at diagnosis and high recurrence after hepatectomy. There is no consensus on treatment for recurrent ICC. We aim to explore predictive factors and treatment outcome for recurrent ICC.

Methods: 160 out of 216 ICC (71.4%) patients experiencing recurrence underwent curative resection from 1977 to 2014. We categorized the recurrent pattern into intra-hepatic involvement (group A, n = 75), locoregional involvement (group B, n = 80), and distant metastasis (group C, n = 65).

Results: Larger tumor size and vascular invasion independently predict ICC recurrence. For group A patients, gross pathological morphology and vascular invasion were the two independent predictive factors. For group B patients, larger tumor size was the only independent predictive factor. For group C patients, larger tumor size and hepatolithiasis were the two independent predictive factors. Further subdivision disclosed patients with merely intrahepatic recurrence had superior overall survival (OS) comparing with those beyond intrahepatic recurrence ($P < 0.0001$). Twenty-seven out of 160 patients underwent repeat hepatectomy or/with metastatectomy for recurrence (16.8%), who had superior OS to the rest 133 patients received other treatment modalities (85.6 versus 20.9 months, $P < 0.001$). Twelve group A patients and 11 group B patients underwent surgery had significantly favorable post-recurrence OS, when compared with those did not (61.6 versus 14.7 and 29.2 versus 8.2 months, respectively, $P < 0.05$).

Conclusions: Aggressive tumor behavior determines high risk of recurrence, however, intrahepatic recurrence may have favorable prognosis. Furthermore, aggressive hepatectomy or/ with metastectomy in selected patients may provide survival benefit in highly selected patients.

PE-225

Efficacy of Sorafenib Alone and in Combination with Rapamycin Inhibitors for Post-Liver Transplant Recurrence of Hepatocellular Carcinoma: A Single Center Experience

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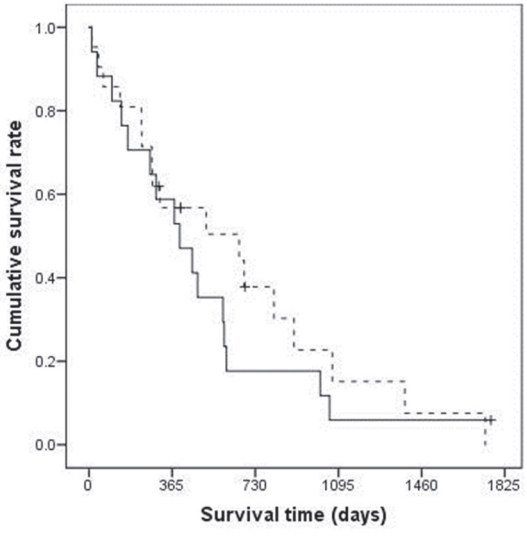
Aims: We investigated the efficacy of sorafenib alone and in combination with a mammalian target of rapamycin (mTOR) inhibitor for the patients with recurrent hepatocellular carcinoma (HCC) after liver transplantation (LT).

Methods: 38 patients, who used tacrolimus as an immunosuppressive agent, diagnosed with recurrent HCC after LT and initiated sorafenib between 2008 and 2019, were retrospectively analysed. Kaplan-Meier analyses were used to calculate progression-free survival (PFS) and overall survival (OS).

Results: The median age of 33 males and 5 females was 53.7 years. 35 (92.1%) and 2 (5.3%) patients had chronic hepatitis B and C, respectively. The median OS from LT was 837.5 days. The median OS and PFS from sorafenib initiation were 453 and 178 days, respectively. 21 patients (55.3%) added mTOR inhibitor with tacrolimus at the time of initiating sorafenib. There was no significant difference of baseline variables whether mTOR inhibitor user or not, except male gender (12 [70.6%] in mTOR inhibitor plus sorafenib user vs. 21 [100%] in sorafenib trestment, $P = 0.012$). The treatment outcomes of sorafenib in combined mTOR inhibitor users were not significantly better compared to sorafenib treatement; the median OS and PFS from sorafenib initiation were 659 (vs. 398) and 230 (vs. 120) days, respectively (All $P > 0.05$).

Conclusions: In a single center experience, combined treatment with sorafenib and mTOR inhibitor was not superior comparing to tacrolimus-mono therapy when perform sorafenib treatment for recurrent HCC after LT.



Keywords: Sorafenib, Rapamycin inhibitor, Liver transplant, HCC recurrence

PE-226

Initial Real-Life Experience of Nivolumab Treatment for Patients with Advanced or Metastatic Hepatocellular Carcinoma after Sorafenib Failure

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Aims: In the checkmate 040 trial, Nivolumab, an anti-PD-1 antibody showed durable response and long-term survival in patients with advanced hepatocellular carcinoma (HCC). We studied this retrospective analysis to evaluate the treatment efficacy and safety of nivolumab in advanced or metastatic HCC after sorafenib failure.

Methods: We retrospectively reviewed the records of HCC patients who had nivolumab treatment at Severance Hospital in Seoul, Korea, between November 2017 and January 2019. Nivolumab 3 mg/kg wad administered. Nivolumab treatment was given every two weeks until progression or intolerable toxicity or death. Response evaluation was done based on mRECIST.

Results: A total of 67 patients entered into this study. We excluded 25 patients who did not perform response evaluation, because of follow-up loss, too short follow-up duration, death. All patients received nivulumab as second-line therapy after progression on sorafenib. The median treatment dose was 8.9 doses. Median overall survival was 9.0 months. The median progression free survival was 3.4 months. One case who had lung metastasis, was complete response, 5 cases partial response, 13 cases stable, and 23 cases progression. The overall response rate (ORR) was 14.3% and disease control rate (DCR) was 45.2%. The most frequent adverse event was Jaundice (21.4%), followed by edema (19%) and nausea (9.5%) and fatigue (9.5%)

Conclusions: In early real-life experience, nivolumab treatment demonstrated clinically meaningful anti-tumor activity and a manageable safety profile in patients with sorafenib-refractory advanced or metastatic HCC.

Keywords: Nivolumab, Hepatocellular Carcinoma, Sorafenib

PE-227

The Risk of Hepatocellular Carcinoma (HCC) after DAA Treatment for Hepatitis C Virus (Clinical Case)

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Aims: Hepatitis B and C virus infections are one of the major causes of liver cirrhosis and HCC in Mongolia. We present a patient with chronic hepatitis C who developed HCC despite sustained virological response and lack of cirrhosis.

Methods: 63 years old women was diagnosed with chronic hepatitis C (genotype 1b, F1) in 2005. Before the treatment HCV RNA was 1845200 IU/ml. She completed a 12-week course of Ledipasvir 90mg/Sofosbuvir 400 mg treatment with sustained virologic response. At baseline and at the end of HCV treatment, computer tomography (CT) scan of abdomen excluded any lesions suspected for HCC. However, alpha-fetoprotein was 35 IU/mL before DAA treatment, increasing up to 152 IU/mL at week-44 of follow-up after the completion of therapy. Transaminase levels were not rising. She was found to have a 1.5 cm, no enhancing hepatic lesion at segment 8 on CT. The lesion was treated with radiofrequency ablation.

Results: Our case suggests that the combination of SVR and less fibrosis may not be fully protective against HCC after DAA treatment. It also raises the issue of how to optimize HCC surveillance after the treatment.

Conclusions: In our case, the increase of alpha-fetoprotein was the first signal. Mechanisms underlying the development of HCC among such patients are still not well-understood and need further investigations

Keywords: HCC, DAA, Mongolia, HCC

PE-228

Hepatocellular Carcinoma in Old Age – Are There Any Benefits of Resection of Liver in Old Age?

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Aims: Hepatocellular carcinoma(HCC) is common cause of death in population. There are some treatment option including surgical resection of HCC, radiofrequency ablation(RFA), or liver transplantation. The number of elderly patients with HCC has been increasing with longer life expectancy of the population. Older people have coexisting medical conditions that can adversely affect surgical outcomes and these become the reason of alternative way including chemotherapy. We compared about the surgical treatment outcomes between older age groups and younger groups.

Methods: We performed 234 hepatic resection in patients with HCC from Mar. 2012 to Dec. 2018. We reviewed retrospectively medical records of patients. Patients divided to two groups. Old age group is more than 70 years old patients and young patients group is less than 70 years old. We compared preoperative, operative characteristics and postoperative outcomes between both groups.

Results: Young age group is 184 patients and old ages is 50 patients. Young patients group had more HBV hepatitis than old age group (61.4% vs 26%), but other indices showed few differences. Two groups had similar number of major resection (26.1% vs 20%), but the operation time was a little bit shorter in old age group. The bleeding during procedure (600cc vs

500cc, median value, $P = 0.285$) and transfusion (both 0cc, median value, $P = 0.337$). The Disease Free Survival(DFS) was 46, 49 each[$P = 0.518$] and Overall survival(OS) was same as 76($P = 0.517$). The major postoperative complications were 23(12.6%) and 9(18.4%) each [$P = 0.351$].

Conclusions: There were no difference between older age groups and younger age groups. Although several risk factors for postoperative morbidity and mortality increase with age, aggressive treatment strategy can achieve long term survival for HCC.

Keywords: Hepatocellular carcinoma, Old age, Surgical approach, Aggressive treatment

PE-229

Postoperative Infectious Complications Decrease Overall and Recurrence-Free Survival in Patients Undergoing Liver Resection for Hepatocellular Carcinoma

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Aims: Postoperative complications greatly impact postoperative course and long-term outcomes in patients who underwent liver resection for hepatocellular carcinoma (HCC). Among them, infectious complications play a relevant role. The aim of this study was to evaluate if postoperative infectious complications impact long-term survival after liver resection for HCC.

Methods: A total of patients undergoing curative liver resections for HCC were retrospectively analyzed from a multi-institutional database. Independent risk factors of postoperative infectious complications were identified. After excluding patients with postoperative early deaths (< 90 days), the long-term overall survival (OS) and recurrence-free survival (RFS) were compared between patients with and without postoperative 30-day infectious complications.

Results: Among 2442 patients identified, 332 had postoperative 30-day infectious complications. Age > 60 years, diabetes mellitus, obesity, cirrhosis, intraoperative blood transfusion, operative time > 180 min and major hepatectomy were identified as the independent risk factors of postoperative infectious complications. In univariable analyses, median OS and RFS of patients with postoperative infectious complications were significantly poorer than those of patients without (86.8 vs. 43.2, and 54.3 vs. 22.6 months, both $P < 0.001$). After adjustment for other prognostic variables, multivariable Cox-regression analyses identified that postoperative infectious complications were independently associated with decreased OS (hazard ratio: 1.199, 95% CI: 1.021-1.660, $P = 0.027$) and RFS (hazard ratio: 1.187, 95% CI: 1.027-1.372, $P = 0.021$).

Conclusions: Postoperative infectious complications decrease long-term OS and RFS in patients undergoing curative liver resection for HCC. To reducing the incidence of infectious complications, preoperative optimization, surgical procedure and postoperative care should be carefully planned.

PE-230

Real-Time Navigation for Laparoscopic Hepatectomy Using Image Fusion of Preoperative 3D Surgical Plan and Intraoperative Indocyanine Green Fluorescence Imaging

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Aims: This study aims to evaluate the feasibility and effectiveness of a novel laparoscopic hepatectomy navigation system (LHNS) that incorporates preoperative three-dimensional models and indocyanine green fluorescence imaging (IGFI) to achieve real-time surgical navigation.

Methods: Forty-eight patients undergoing laparoscopic hepatectomy from January 2017 to December 2018 were selected. 23 patients were performed under the guidance of LHNS, and 25 were treated with laparoscopic hepatectomy. The operative condition and clinical prognosis were analyzed retrospectively.

Results: There was no significant difference in preoperative characteristics between the two groups. There was no statistical difference between the two groups in the operation and clinical results. The hepatic tangent line was clearly displayed by LHNS in 20 cases; however, the boundary projection was unclear in 2 cases and the boundary was not clearly displayed in 1 case with IGFI. In addition, unexpected bleeding caused by injury to important pipelines was avoided by the projection of three-dimensional models of blood vessels during incision of hepatic parenchyma.

Conclusions: The LHNS we developed provides a new intraoperative image guidance method for laparoscopic hepatectomy. The results of our comparative analysis confirmed the feasibility and clinical utility of LHNS in identifying intrahepatic anatomy, determining the scope of hepatectomy and guiding hepatic parenchymal disconnection in real time. LHNS is expected to become a new real-time navigation system for laparoscopic hepatectomy.

PE-231

Three-Dimensional Visualization Evaluation and VR Study of Giant Liver Cancer with Blood Vessels as the Axis

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Aims: To explore the clinical application value of three-dimensional visualization of blood vessels as the axis and virtual reality technology in giant liver cancer.
Methods: The thin-layer CT image data of 13 patients who were diagnosed as giant primary liver cancer by medical history, imaging and laboratory tests were collected for three-dimensional reconstruction, and then transformed into VR model. The anatomical relationship between the tumor and its surrounding important structures was analyzed. The preoperative evaluation, typing and surgical planning based on blood vessels as the axis were carried out to guide intraoperative navigation. The consistency was verified by the intraoperative rapid pathological examination.
Results: 13 patients successfully achieved 3D reconstruction and VR model transformation. According to the 3D visualization classification of blood vessels as the axis, 13 cases were as follows: 3 cases of type I a grade 1, 2 cases of type Ⅰ a grade 2; 1 case of type Ⅱ a grade 2; 1 case of type Ⅱ b grade 3; 2 cases of type Ⅱ c grade 3; 4 cases of type Ⅱ a grade 3.
Conclusions: Three-dimensional visualization and VR technology can provide comprehensive information on the anatomical structure of liver cancer lesions and blood vessels, which is of great value in the application of giant liver cancer surgery.

PE-232

Application of Three-Dimensional Visualization, VR Technology Combined with ICG Molecular Fluorescence in Hepatectomy under Non-Vascular Occlusion for Centrally Located Hepatocellular Carcinoma

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Aims: To explore the application value of three-dimensional visualization, VR technology combined with ICG molecular fluorescence in hepatectomy under non-vascular occlusion for centrally located hepatocellular carcinoma.
Methods: Clinical data of one patient with centrally located hepatocellular carcinoma undergoing mesohepatectomy in the Department of Hepatobiliary, Zhujiang Hospital Affiliated to Southern Medical University in July 2018 were retrospectively analyzed. Three-dimensional visualization and VR technology were adopted and intraoperative use of FIGFI was combined with hepatectomy under non-vascular occlusion.
Results: According to the three-dimensional visualization, the volume of the whole liver, the tumor, the pre-resected liver and the residual liver was 1423.54ml, 405.35ml, 524.48 ml and 899.06 ml respectively. The residual liver volume accounts for 63.15% of the standard liver volume. The tumor was about 11.1*11.5*8.54 cm. VR model showed that the tumor was located in segments Ⅵ, Ⅴ and Ⅷ. Three-dimensional visualization with blood vessels as the axis was classified as 3-class, Ⅱ b-type. The centrally located hepatocellular carcinoma was classified as type Ⅲ, which was to be treated by mesohepatectomy. Mesohepatectomy under non-vascular occlusion was performed during operation. The preoperative 3D visualization and VR model were consistent with the intraoperative findings, and the preoperative planning was consistent with the actual operation. There were no obvious postoperative complications.
Conclusions: Three-dimensional visualization and VR technique combined with ICG molecular fluorescence can assist hepatectomy under non-vascular occlusion for centrally located hepatocellular carcinoma.

PE-233

Is the Outcome after Hepatectomy for Hepatocholangiocarcinoma Different from That of Classic Hepatocellular Carcinoma and Mass-Forming Cholangiocarcinoma? A Case-Matched Analysis

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Aims: Hepatocholangiocarcinoma (HCC-CC) is a rare tumor. The aim of this study was the analysis of the outcome comparing such tumor with classic hepatocellular carcinoma (HCC) and mass-forming cholangiocarcinoma (MFCCC).
Methods: Our prospectively maintained database was queried, and 20 patients with HCC-CC were identified. A 2:1 match was performed with 40 patients operated in the same period for HCC, and with 40 operated for MFCCC. Only T1 or T2 patients N0 M0 were considered. Primary endpoint was the overall survival (OS) and disease-free survival (DFS).
Results: Median tumor diameter of HCC-CC group was 3.8 cm (range 1.3-5), and single tumor was detected in 13. After a median follow-up of 33.8 months (range 6-77), the 1-, 3-, and 5-year OS rates were 90%, 65%, and 50% respectively. The 1-, 3-, and 5-year DFS rates were 65%, 45%, and 20% respectively. Both OS and DFS did not differ significantly among the three histotypes.
Conclusions: Patients with HCC-CC showed similar rates of OS and DFS to those patients with classic HCC and MFCCC. Further evaluations of differences in tumor features and biology are necessary to better characterize the prognosis of patients with HCC-CC.

PE-234

ALPPS versus Two-Stage Hepatectomy (TSH): Indications, Safety, Efficacy

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Aims: The aim of this study was to compare the clinical changes associated with ALPPS and PVL and assess the oncological outcomes.

Methods: Retrospective analysis of 30 patients with CRLM and HCC operated with ALPPS or PVL at the abdominal department. After analysis of the whole cohort, both groups were matched and analyzed.

Results: Fifteen patients age 57±11.6 yr were operated by PVL techniques for 5±3 (2-10), metastases of which the largest was 58±27 MM. ALPPS was initiated for 2.8±1.6 metastases of which the largest was 64.6±18.8 mm in 15 patients whose mean age was 59±6.3yr. One patient had salvage ALPPS after failed PVL. The time between two steps was 72.3±32.8 days for PVL and 9.4±1.4 days for ALPPS, FLR increased by 59.5±65.9% vs 95.1±53.6 ($P < 0.001$) respectively. The second stage of PVL was performed in 73.3% patients, ALPPS-2 in 86,7%. Major complication (Clavien ≥IIIb) rates were 0% vs. 9,1% in the PVL and ALPPS group, respectively. There was 2 (15%) postop death after ALPPS-1 due to hepatic failure in the patients who had a HCC and liver cirrhosis. The overall survival of the ALPPS group was significantly lower than that of the PVL(26,1mo vs. 44.0mo, $P = 0.021$), as well as disease-free survival (24,1mo vs. 39,4mo, $P = 0.011$).

Conclusions: The ALPPS technique can be associated with a hypertrophic stimulus on the future liver remnant stronger than other techniques–such as portal vein ligation at early terms. Meanwhile, the survival following ALPPS was significantly lower than that posterior to PVL.

PE-235

ALPPS Procedure in 20 Patients with Primary and Metastatic Malignancies: Single Centre Experience

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Aims: The main goal was to assess safety and outcomes of ALPPS procedure and find the optimal compromise between dropout and mortality risk, using our initial single-center experience.

Methods: 20 patients who have underwent ALPPS resection at the abdominal surgery department Moscow Oncological Research Institute n.a. P.Hertsen from January 2012 to June 2016 were retrospectively analyzed. Multivariate logistic regression analysis was performed to identify independent risk factors for severe complications, mortality and volume growth of the FLR.

Results: Mean age was 59,1±6,3 (49 -72) years. Indications for surgical resection were CRLM in 80% cases and HCC in 20% cases. One patient had salvage ALPPS after failed PVL. Patients were operated for 2.8±1.6 metastases, the largest was 64.6±18.8 mm(40-104). The increase in FLR between the two procedures was 95.3±53.6% (range: 13-164%, $P < 0.001$). The average time between steps of the procedure was 9.4±1.4 days. Severe complications including mortalities (Clavien-Dindo≥IIIb) occurred in 6,7 and 9,1% of patients after ALPPS-1 and 2 respectively. Follow-up mediana was 20 mo. Medium overall survival rate was 26,1 [22,5-29,6] mo. Medium disease-free survival 24,1 [19,6-28,5]mo.Primary liver cancer, age, histologic changes of liver parenchyma, led to morbidity and mortality rate.

Conclusions: ALPPS should be reserved to a small proportion of patients, the young ones with very small future liver remnant, with the low rate of liver function reserve or experiencing inadequate hypertrophy after portal vein occlusion. For these patients ALPPS could still offer a benefit, being the only chance of resectability.

PE-236

Surgical Tactics for Colorectal Cancer with Synchronous Liver Metastases

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Aims: Comparative assessment of the immediate results of simultaneous removal of the primary colorectal tumor with liver resection and two-step operations.

Methods: The results of treatment of 36 patients from 2010 to 2018 were analyzed. 15 simultaneous and 21 consecutive operations were performed for synchronous colorectal metastases in the liver. Of these, extensive liver resections were performed in 41.7% and 58.3% of cases, respectively. Clinical, intraoperative, postoperative data were analyzed to assess the immediate results of the treatment.

Results: Simultaneous operations did not increase intraoperative blood loss (756 ± 76 against 835 ± 83 ml, $P = 0.4$), the number of postoperative complications (6.6% against 3.8%) and mortality (0% against 2.9% (1 patient)) in comparison with sequential operations. During operations on the colon and rectum, the number of postoperative complications and mortality did not differ ($P = 0.61$ and $P = 0.48$, respectively). Comparative assessment of postoperative complications and mortality after extensive simultaneous and sequential operations also revealed no differences ($P = 0.93$ and $P = 0.96$, respectively). All patients received adjuvant chemotherapy according to the XELOX, FOLFOX scheme.

Conclusions: If simultaneous intrahepatic metastases of colorectal cancer are detected and there are no marked associated diseases, it is advisable to perform simultaneous operations,

regardless of the location of the primary tumor and the amount of liver resection.

Keywords: Liver metastasis, Colorectal cancer, Liver resection, Simultaneous operation

PE-237

Immediate Results of Surgical Treatment Hepatocellular Cancer

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Aims: To evaluate the immediate results of surgical treatment of HCC.

Methods: The results of treatment of 25 patients with hepatic HCC from 2010 to 2018 are analyzed. There were 14 men (56.0%), women-11 (44.0%). The average age of patients was 61 ± 9 years. In 9 patients, the formation is localized in the left lobe, in 13 in the right lobe and 3 patients with bilobar liver damage.

Results: The following types of liver resection were performed: RHHE –13, LHHE - 9, LLE - 1, exploratory laparotomy - 2. Blood loss averaged 798 ± 256 ml., minimum 200 ml. According to the international classification of TNM, patients were distributed as follows: T2N0M0 (stage I) - 19, T3N0M0 (stage II) - 6, T4N1M0 (stage IV) - 1 patients, There were the following types of complications in the postoperative period: hepatic failure in 6th, received conservative therapy; in 2 patients, the formation of a biloma in the abdominal cavity, followed by drainage under local anesthesia, received conservative treatment. One patient has a biliary fistula, closed on the 14th day after the operation. Postoperative mortality was not observed.

Conclusions: The presence of cirrhosis and hepatitis in patients with hepatic HCC worsens the immediate and long-term results of treatment, but is not a contraindication to surgical treatment. Surgical treatment of HCC requires an accurate preoperative assessment of the functional reserve of the liver.

Keywords: Hepatocelular cancer, Liver resection, Surgical treatment, Immediate results

PE-238

The Current Status of Selecting Treatment Modalities for Naïve Hepatocellular Carcinoma Patients over 70 Years Old: Single-Center Experience

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Aims: There are still some controversies on optimal therapeutic options for hepatocellular carcinoma(HCC) patients who were over 70 years old. This study evaluated the current status of treatment modalities for naiive elderly HCC patients in single-center to determine optimal management strategy.

Methods: From January 2014 to December 2016, we reviewed medical records of 280 naiive HCC patients over 70 years old who visited the Hepatoma Clinic in Severance Hospital, Seoul, Korea. Clinicopathological data and survival analysis were analyzed.

Results: Among these patients, 39.3% of them were Hepatitis B carrier and 75% of them had been previously diagnosed as liver cirrhosis. 65 of 280 patients(23.2%) underwent surgical resection who mostly considered as single lesion (95.4%), and all 65 patients obtained R0 resection. For the patients aged 70-75 years old, 26.9% of them underwent surgical resection, and 48.7% of them received transarterial therapy. For the patients over 80 years old, 6.7% of them underwent surgical resection, and 82.2% of them received transarterial therapy. There were statistically significant differences in selection of treatment between two groups. The overall survival and disease-free survival analysis showed a statistically significant superiority of surgical resection compared with transarterial therapy. In the propensity score matching analysis of the surgical and transarterial therapy group, there was no significant difference between the two groups in overall survival and disease-free survival.

Conclusions: Although transarterial therapy is most common treatment of choice in elderly naiive HCC patients, adequate surgical resection is another important therapeutic option to consider in achieving survival benefit in treating HCC.

PE-239

A Current Status of Therapeutic Choice and Feasibility for Hepatocellular Carcinoma Patients over 70 Years Old

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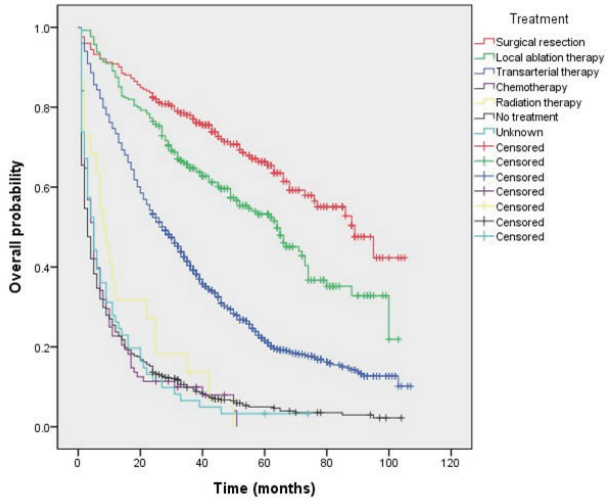
Aims: Hepatocellular carcinoma (HCC) is the third most common cancer in the digestive system based on survey of domestic cancer incidence, and the ratio of elderly aged 65 or older is expected to rise steadily, leading to a higher incidence of total hepatocellular carcinoma. Benefit of treatment should be greater than the reduction of survival period or maladjustment due to treatment. Based on these perspectives, we investigated how the detailed treatment of hepatocellular carcinoma in elderly patients and overall survival of each treatment modalities.

Methods: From January 2003 to December 2005 and January 2008 to December 2014, the National Cancer Center (NCC) and Korean Liver Cancer Study group (KLCSG) collected 3,006

clinical datas from HCC patients over 70 years old investigating Korea Central Cancer Registry (KCCR) receords at 54 medical centers in south Korea.Using this data we analyzed current treatment modality and overall survival of each modalities in treating HCC patients over 70 years old.



Results: In Period 2003-2005, there were 578 patients and in period 2008-2014, 2428 patients were analyzed. Transarterial therapy (period 2003-2005 : 49.1%, period 2008-2014 : 44.4%) was the most commonly used treatment modality. Among them, Transarterial chemoembolization (TACE) with gelatin sponge occupied largest proportion (96.1%, 65.6%). In overall survival analysis, surgical resection showed statically significant superiority than other treatment modalities ($P < 0.001$), followed by local ablation therapy and transarterial therapy in both periods. Other modalities showed no statistical differences including no treatment. Among transarterial and chemotherapy, there are no statistically significant differences between transarterial therapy modalities except sorafenib. However, there were no statistically significant differences in propensity score matching for surgical resection, local ablation therapy, and transarterial therapy for relatively early stage lesions. In subgroup analysis, there was statistically significant difference between the surgical resection, local ablation therapy, transarterial therapy and the rest of other treatment modalities in the 70-75 year period. However, there was no significant difference between surgical resection, local ablation therapy, transarterial therapy in the ages of 75-80 years and over 80 years period.

Conclusions: Transarterial therapy was the most commonly used treatment modality in HCC patients over 70 years old, however surgical resection showed statistically significant superior overall survival rate than other modalities.

Keywords: Hepatocellular carcinoma, Surgical resection, Elderly, Transarterial therapy

PE-240

Survival According to Recurrence Patterns after Resection for Transplantable Hepatocellular Carcinoma in HBV Endemic Area: Appraisal of Liver Transplantation Strategy

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Aims: Progress in antiviral treatment for chronic hepatitis B patients and hepatocellular carcinoma (HCC) screening program has increased the number of early stage HCC. Liver resection (LR) or transplantation (LT) can be performed with curative intent for early stage HCC but in the era of liver donor shortage, effective treatment allocation strategies is required. Therefore, survival outcomes according to recurrence patterns after LR were analyzed to determine the feasibility of salvage LT.

Methods: During 2004-2016, 468 patients diagnosed with HCC within Milan criteria (MC) and child Pugh grade A who had liver resection as initial treatment were analyzed. Survival outcome were analyzed according to the recurrence patterns.

Results: The study included early HCCs with 6.2% of satellite nodule, 21.6% of microvascular invasion, 89.1% of single tumor, 64.1% with tumor size ≥2 cm, and 42.7% of high grade tumor (Edmonson grade III-IV). During median follow-up duration of 59 months, recurrences occurred in 211 patients, 175 (37.4%) recurrences within MC and 36 (7.7%) recurrences beyond MC. Majority of HCC recurrence beyond MC developed within 2 years (77.8%). Independent predictors of recurrence beyond MC that disabled salvage LT were presence of satellite nodules, microvascular invasion, and unfavorable gross finding (multinodular confluent and infiltrative) (all, $P < 0.05$). All patients with three risk factors showed recurrence and the highest cumulative incidence of mortality. The 5-year overall survival was the lowest in recurrence beyond MC (26.5%) group followed by within MC (86.6%) and no recurrence groups (95%), $P < 0.001$. Among patients who recurred within MC, locoregional therapies (LRTs) were performed in 131 (75%) patients which led to disease free survival of 30 months.

Conclusions: Recurrence beyond MC occurs in minority of patients with early stage HCC and preserved liver function. Furthermore, LRTs were able to prolong DFS in patients that recurred within MC allowing sufficient time until salvage LT. Our data provides rationale for liver resection first followed by prophylactic LT when there is recurrence in the view of organ shortage.

Keywords: Hepatocellular carcinoma, Salvage liver transplantation, Liver resection, Milan criteria

PE-241

The Meaning of Enhanced Liver Fibrosis (ELF) Score as a Predictive Factor for HCC Patient after Liver Resection

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Aims: The enhanced liver fibrosis (ELF) score is and extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) having good correlations with fibrosis stages in chronic liver disease. Moreover, elevated ELF score has been suggested as a poor prognostic factor for cholangiocarcinoma probably related to tumor's desmoplastic nature. Thus, this study aimed to figure out the predictive value of ELF score for the hepatocellular carcinoma (HCC) patients having liver resection.

Methods: From Aril 2015 to December 2018, preoperative ELF score was collected for 62 patients with HCC having curative liver resection. The patients were grouped according to ELF score as 10 and perioperative outcome was compared. Perioperative prognostic factors were also analyzed for disease-free survival after liver resection.

Results: Patients group over 10 of ELF score had significantly higher liver stiffness by transient elastography (8.26 ± 3.28 Vs 17.60 ± 14.52 Kpa, $P = 0.004$), lower platelet count (190.91 ± 51.10 Vs, 149.53 ± 70.56 x 10^3/mm^3, $P = 0.01$) lower serum albumin level (4.47 ± 0.35 Vs 4.06 ± 0.37 g/dL, $P < 0.001$), and higher AST level (30.20 ± 9.80 Vs 45.22 ± 20.97, $P = 0.002$). Liver stiffness over 14 kPa and ELF over 10 were significant prognostic factors for disease-free survival ($P = 0.042$ and 0.030, respectively). ELF over 10 was the significant prognostic factors on multivariate analysis (relative risk with 95% CI= 2.795 (0.989 ~ 7.903), ($P = 0.053$).

Conclusions: Higher ELF score may be correlated with poor liver condition correlating liver fibrosis. Moreover, ELF score was the only significant prognostic factor for disease-free survival for the patient having HCC after liver resection.

Keywords: ELF, HCC, Liver resection, Predictive factor

PE-242

Long-Term Post-Resection Prognosis of Primary Neuroendocrine Tumors of the Liver

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Aims: Primary hepatic neuroendocrine tumor (PHNET) is a very rare neoplasm, requiring strict exclusion of metastasis from possible extrahepatic primary sites for its diagnosis.

Methods: We reviewed our clinical experience of 13 patients with hepatic primary NET who underwent hepatic resection from January 1997 to December 2015.

Results: The mean age of 13 patients was 51.1±12.8 years, with 8 males and 5 females. The most common clinical manifestation was vague nonspecific abdominal pain (n = 9). Of them, 7 patients underwent preoperative liver biopsy, which was correctly diagnosed as neuroendocrine tumor (NET) in 4. Ten patients R0 resection and 3 underwent R1 resection. Diagnosis of hepatic primary NET was confirmed immunohistochemically and by absence of extrahepatic primary sites. All tumors were single lesions, with size of mean 9.6±7.6 cm and median 4.3 cm. All showed positive staining for synaptophysin and chromogranin. During a mean follow-up of 95.1±86.6 months, 7 patients died from tumor recurrence, whereas the other 6 remain alive to date, making the 5-year tumor recurrence rate 56.0% and the 5-year patient survival rate 61.5%. When confining to R0 resection, 5-year recurrence and survival rates were 42.9% and 70.0%, respectively. Univariate analysis showed that Ki-67 proliferative index was the only risk factor for tumor recurrence.

Conclusions: PHNET is a very rare tumor with no specific clinical features. Final diagnosis of PHNET depends mainly on pathology and immunohistochemistry and exclusion of metastasis from other sites. Active surgical treatment is effective for PHNET because of acceptably favorable post-resection outcomes.

Keywords: Neuroendocrine tumor, Metastasis, Resection, Diagnosis

PE-243

Development and Validation of Novel Scoring System for the Prediction of Disease Recurrence Following Resection of Colorectal Liver Metastasis

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Aims: The aim of this study was to identify predictive factors for the recurrence of colorectal cancer liver metastasis(CRLM) and then to develop a corresponding novel scoring system that should improve the sensitivity of predicting recurrence in patients with CRLM.

Methods: A total of 295 consecutive CRLM patients were enrolled in our institution between January 2002 and December 2015. Multivariate analyses were performed to identify the variables associated with disease recurrence and established the

novel scoring system based on it.
Results: The scoring system considered seven variables: synchronosity, CA19-9 level, number of liver metastasis, largest size of liver metastasis, resection margin of hepatic lesion, neutrophil-to-lymphocyte ratio and prognostic nutritional index. The area under the curve of ROC was 0.824 (95% confidence interval 0.767–0.882); the sensitivity of our scoring system was 87.9%, specificity was 66.7%, positive predictive value was 20.6%, and negative predictive value was 20.9%.
Conclusions: For patients with CRLM undergoing curative hepatic resection, our novel scoring system would improve the sensitivity for prediction of disease recurrence in Case of CRLM patients.

PE-244

Surgical Strategies of Huge Hepatocellular Carcinoma with Main Portal Vein Thrombosis: A Case Report

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Aims: Huge hepatocellular carcinoma (HHCC) is commonly considered tumor diameter over 10 cm. The prognosis of HHCC or HCC with PVTT was poor, many investigator performed non-surgical treatment. But some study reported that aggressive operation for HHCC with PVTT brought good results and prognosis compared to non-surgical interventions.
Methods: 46 years old, HBV carrier man was referred to our hospital for hepatic mass. In laboratory test, platelet counts: 80,000, PT: 1.17 INR, total bilirubin: 1.61mg/dl, GOT/GPT: 32/12, Cr: 0.49, albumin: 3.9g/dl, AFP: 76,430, PIVKA-II: 1478.78. In radiologic examinations, HHCC (11 cm) abutting middle hepatic vein (HV) was located in right hepatic lobe and combined with PVTT from right PV to main PV.
Results: We performed right hepatectomy and PV thrombectomy. Surgical procedures were summarized as follows; (1) cholecystectomy; (2) right, left and main PV and right hepatic artery (HA) were respectively isolated and hung with vessel loops after hepatic hilar dissection; (3) left and main PV were clamped by vascular clamps for protection thrombosed propagation; (4) right PV was transversely opened, and then PV thrombectomy was performed; (5) right PV and HA was ligated; (6) right liver was mobilized and right HV was isolated and ligated; (7) after blocking off hepatic inflow and outflow, right hepatectomy was performed by CUSA system.
Conclusions: In conclusion, surgical strategies of HHCC with main PVTT is that we initially perform PV thrombectomy while preserving hepatic side PV is clamping, and then ligate removed side HA, PV and HV for protection of tumor propagation during hepatic manipulation and resection.

PE-245

Outcomes after Robotic Donor Hepatectomy in 48 Consecutive Live Donors

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Aims: Laparoscopic donor right hepatectomy has been performed in a few centers by expert surgeons. Robotic system is one of the tools for laparoscopic liver resection, however, there have been few studies about surgical outcomes after robotic living donor hepatectomy, especially for a right graft.
Methods: From Apr. 2016 to Jan 2019, 48 liver donors received robotic donor hepatectomy (45 right grafts, two left grafts and one left lateral graft) in our institute. Short-term outcomes were evaluated in a prospective way.
Results: The median age of donors was 29.1 years and 24 donors were male. The mean right graft volume was 714.0 ml (range, 517-919). The mean operative time and blood loss were 500 min and 112.4 ml, respectively. The median warm ischemic demarcation time was 14 min. The first case was converted to mini-laparotomy (2.1%) due to injury to the left bile duct.There were three events related to hem-o-lok including dislodgement from the right bile duct, the inferior hepatic vein and the right hepatic artery. The first two events were managed during the operation, but an emergency laparotomy was needed to control bleeding from the right hepatic artery. Postoperative complications occurred in eleven patients and severe complication more than grade III occurred in two patients (one hepatic artery bleeding and one bladder injury). The mean hospital stay was 9 days.
Conclusions: From our experience, robotic living donor hepatectomy is feasible and safe at expert hands in selected liver donors. However, hem-o-lok should be cautiously used due to the possibility of the dislodgement.

PE-246

Synchronous Resection of Colorectal Cancer Liver Metastasis: Propensity Score Matching of Open Versus Minimally Invasive Surgery

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Aims: Synchronous open liver resection of colorectal cancer liver metastasis has demonstrated safety, efficacy and feasibility in several studies. Nevertheless, still oncologic safety and perioperative outcome of synchronous minimally invasive liver resection in colorectal cancer liver metastasis remain unclear.
Methods: From January 2006 to June 2017, we reviewed synchronous liver resection in colorectal cancer liver metastasis patients in Severance hospital. We exclude hybrid resection. Eventually, 391 patients were investigated.

Results: Total 66 patients underwent pure minimally invasive approach for liver resection and primary cancer operation. On the other hand, 325 patients was performed open liver resection. Between two group, length of stay(LOS, 14.7 days vs 9.7 days) and imaging liver metastasis lesion numbers (3.9 vs 1.5) and final pathologic liver metastasis number (3.8 vs 1.4), tumor size (2.8 cm vs 1.9 cm) were statistically higher in open group. In survival analysis, minimally approach for liver resection group was more favorable than open resection group in overall survival (mean 87.9 months vs 110.9 months, $P = 0.011$) and disease free survival (mean 40.6 months vs 59.3 months. $P = 0.033$). After propensity score matching, LOS of still longer in open resection group in statistically significance. In survival analysis, there were no differences between two groups.
Conclusions: Syncrhonous minimally invasive liver resection for colorectal cancer liver metastasis is safe and fesasible with benefit of short LOS. In terms of oncologic outcome, minimally invasive liver resection was not inferior to open liver resection. In selected patients, minimally invasive approach for liver metastasis resection synchronously should be considered.

PE-247

Treatment of Resectable Hilar Cholangiocarcinoma: A Choice of Right- or Left-Side Hepatectomy

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Aims: Radical resection is the only curative treatment for patients with hilar cholangiocarcinoma. This study aimed to compare the surgical morbidity and long-term outcome between right- and left-side hepatectomy to help the decision of which side of liver to be resected in the surgical treatment of hilar cholangiocarcinoma.
Methods: A total of 83 patients attempting surgical resection for hilar cholangiocarcinoma at the Korea university medical center between 2010 and 2017 were considered for this study. After excluding patients who did not undergo curative-intent surgery or hepatectomy, 57 patients undergoing right- or left-side hepatectomy were finally enrolled for analysis. Prospectively collected clinicopathologic characteristics, perioperative outcomes and survival were evaluated.
Results: Right-side hepatectomy (RH) and left-side hepatectomy (LH) were performed for 33 and 24 patients, respectively. The proportion of R0 resection was comparable between both groups (66.7% for both RH and LH groups, $P = 0.616$). Posthepatectomy liver failure was significantly more prevalent in the RH group than LH group (75.7% vs. 12.5%, $P < 0.001$). The 90-day mortality was not differ between both groups (9.1% vs. 4.2%, $P = 0.631$). The 5-year overall survival rates were 37.7% for the RH group; and 41.9% for the LH group ($P = 0.500$). The 5-year recurrence-free survival rates were 26.3% for the RH group; and 33.9% for the LH group ($P = 0.580$).
Conclusions: Posthepatectomy liver failure was more prevalent in the RH group than LH group, but it did not affect the 90-day mortality. It is recommended to perform surgical resection only according to the possibility to achieve radical resection, regardless of right- or left-side hepatectomy.

PE-248

Hypothermic Perfusion Hepatectomy for Unresectable Liver Cancer: A Single-Center Experience

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Aims: Despite technical advancements in liver surgery, resection of liver tumors that involve the hepatic veins adjacent to the vena cava or hepatic hilum remains technically challenging. We present our surgical techniques and the long-term outcome of 5 patients with conventionally unresectable tumors.
Methods: Between September 1999 and March 2016, we encountered 5 patients with conventionally unresectable tumors that were successfully treated by "ex-situ liver resection" and "in-situ & ante -situm hypothermic liver perfusion" under total vascular exclusion and venovenous bypass.
Results: These approaches allowed complete tumor removal with vascular reconstruction under a bloodless operation field, while minimizing hepatic ischemic injury and preserving liver function. No perioperative mortalities occurred and postoperative complications were minimal. The postoperative survival periods were limited due to the advanced malignancies in our patients, but the survival benefit was encouraging. The median postoperative survival time was 29.1 months, with the longest survival period being nearly 10 years. Furthermore, these approaches improved the quality of life and provided our patients with an opportunity for additional treatment.
Conclusions: Hypothermic perfusion hepatectomy is a realistic option for achieving surgical cure or significantly improved survival and quality of life in patients with tumors deemed unresectable using conventional normothermic hepatectomy. These approaches can overcome the limitations of the liver's restricted normothermic ischemia tolerance or inaccessible tumor locations.

PE-249

Prognostic Analysis of Hepatocellular Carcinoma Greater than 5 cm in Diameter after Curative Resection

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Introduction: This study aimed to evaluate the impact of hepatocellular carcinoma (HCC) greater than 5 cm to the recurrence

pattern and the prognosis after hepatectomy.
Methods: 55 patients who underwent hepatectomy (Open 47 and Laparoscopic 8) for HCC > 5 cm without major vascular invasion from 2008 to 2018 at single institute were retrospectively analyzed. We divided two groups such as 5 cm < HCC < 10 cm or huge HCC ≥10 cm (hHCC).
Results: The level of alpha-feto protein and PIVKA with 5 cm < HCC < 10 cm (n = 44) (1369ng/ml and 3278mAU/ml) were lower than those of patients with hHCC (n = 11) (19128ng/ml and 3761mAU/ml). Pathologically, hHCC showed more frequent than 5 cm < HCC <10 cm with microvessel and intrahepatic invasion (100 and 55% versus 71.8 and 25%). The overall survival and DFS (disease free survival) of patients with hHCC (38 and 20.2 months) were significantly worse than those of patients with 5 cm<HCC <10 cm (40.25 and 22.8 months). The intra/extra hepatic recurrence rate showed 36% (16), 2% (1) with 5 cm < HCC < 10 cm and 27% (3), 27% (3) with hHCC. Both group has an independent risk factor for extra-hepatic recurrence (Hazard ratio 7.86, P<0.005). The DFS of patients with extra-hepatic recurrence was worse than patients with intra-hepatic recurrence. (13.3 and 14.6 months).
Conclusions: In our study, the extra-hepatic recurrence is an independent risk factor in HCC greater than 5 cm in diameter. Especially, hHCC has higher rate of extra-hepatic recurrence and lower DFS.

PE-250

Preoperative Glasgow Prognostic Score (GPS) as a Predictor of Poor Prognosis in Synchronous Colorectal Cancer Liver Metastasis

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Aims: Recently, the Glasgow prognostic score (GPS) and the modified GPS(mGPS), an inflammatory response marker, have been reported to be associated with the prognosis in patients with various type of cancer. We investigated the value of the GPS and mGPS for the predictor of prognosis in patients with synchronous liver-limited colorectal metastases (sCRLM).
Methods: Eighty-three patients who histologically diagnosed as sCRLM were selected. Their laboratory and clinical data were collected retrospectively. We calculated the GPS and mGPS. Univariate and multivariate analysis were performed to examine the score on overall survival and disease free survival.
Results: Length of hospital stay was significantly correlated with high mGPS (P = 0.038). The multivariate analysis identified the GPS as independent prognostic factors for OS and DFS in all patients (P = 0.021, P < 0.001). Patients with high mGPS had a significantly longer OS and DFS (P = 0.048, P < 0.001).
Conclusions: In conclusion, elevated preoperative GPS and mGPS is correlated with both survival and disease free survival in patients who have been diagnosed with resectable sCRLM.

PE-251

Computed Tomograph Imaging Features and Early Response of Hepatocellular Carcinoma Treated by Transarterial Chemoembolization with Drug Eluting Beads

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Aims: To describe imaging features and evaluate tumor response to first session of transarterial chemoembolization (TACE) with drug-eluting beads (DEB) in patients with hepatocellular carcinoma.
Methods: In this prospective study, 78 HCC patients were treated with one session TACE using Doxorubicin-eluting Bead. CT was performed in all patients before treatment and from 1 to 3 months after the procedure. Imaging response was evaluated according to the modified Response Evaluation Criteria in Solid Tumours (mRECIST).
Results: Records of 78 patients were reviewed. Mean age was 60.5 ± 10.1. Male was 89.7%, female was 10.3%. Child-Pugh severity rate: Child A 94.9%, Child B 5.1%. BCLC score: stage B 88.5%, stage C 11.5%. Most tumors located in the right lobe 79.5%. The number of tumor: single 37.2%, multiple 62.8%. Size of tumor rate < 5 cm: 14.1%, 5-10 cm: 55.1%, >10 cm: 30.8%. In hepatic arterial phase, there was the most enhancement with mean 84.4 ± 32.8 (HU). 11.5% patients had branch portal vein thrombosis. After one session of treatment with TACE, the mean size of tumor decreased from 8.8 ± 3.6 cm to 7.2 ± 3.8 cm, P = 0.001. The rate of complete response was observed in 25.6%, partial response 47.4%, stable disease 20.5% and progressive disease 6.4%.
Conclusions: Computed tomography imaging is helpful method for guiding the selection of an optimal treatment strategy and assessing the tumor response to treatment in patients with HCC.
Keywords: Transarterial chemoembolization, Computed tomograph, Hepatocellular carcinoma

PE-252

Clinical Outcomes after Risk-Adapted Proton Beam Therapy Using Three Dose-Fractionation Regimens for Hepatocellular Carcinoma

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Aims: The aim of this study was to evaluate the long-term efficacy and safety of risk-adapted PBT in patients with hepatocellular carcinoma (HCC).

Methods: Inclusion criteria for the present study were: i) HCC was diagnosed by pathologic confirmation or radiologic findings according to the guidelines of the Korean Liver Cancer Study Group and the National Cancer Center; ii) HCC lesions were unsuitable, ineffective, or refused for any other loco-regional treatments; iii) patients were treated with risk-adapted PBT using three dose-fractionation regimens depending on the proximity of the GI organs; iv) there was no uncontrolled intrahepatic disease outside of the targeted lesion; v) liver function of Child-Pugh class A or B7 was present; and vi) no extrahepatic metastasis. Between June 2012 and April 2017, 243 patients who met all of the inclusion criteria were analyzed in present study. Three dose-fractionation regimens were used according to the proximity of the gastrointestinal (GI) organs: (1) regimen A, the prescribed doses to planning target volume (PTV)1 and PTV2 were 50 GyE (EQD2, 62.5 GyE_{10}) and 30 GyE (EQD2, 32.5 GyE_{10}) in 10 fractions, 5 fractions a week, respectively, for the patients with GTV<1 cm from the GI organs; (2) regimen B, the prescribed doses to PTV1 and PTV2 were 60 GyE (EQD2, 80 GyE_{10}) and 30 GyE in 10 fractions, respectively, for the patients with GTV within 1-1.9 cm from the GI organs; and (3) regimen C, the prescribed dose to PTV1, identical to PTV2, was 66 GyE (EQD2, 91.3 GyE_{10}) in 10 fractions for the patients with GTV≥2 cm from the GI organs.

Results: In all patients, the 5-year local recurrence-free survival (LRFS) and overall survival (OS) rates were 87.5% and 48.1%, respectively, with grade ≥3 toxicity of 0.4%. In regimens A, B, and C, the 5-year LPFS and OS rates were 62.4%, 94.7%, and 92.4% ($P < 0.001$), and 16.7%, 39.2%, and 67.9% ($P < 0.001$), respectively. The 5-year OS rates of the patients with mUICC stages I, II, III, and IVA and BCLC stages A, B, and C were 69.2%, 65.4%, 43.8%, and 26.6% ($P < 0.001$), respectively and 65.1%, 40%, and 32.2% ($P < 0.001$), respectively. In a multivariate analysis, the Child-Pugh classification, alpha-fetoprotein level, mUICC stage, dose-fractionation regimens, and primary tumor response were independent prognostic factors associated with OS.

Conclusions: Risk-adapted PBT using three dose-fractionation regimens could achieve promising long-term tumor control across all stages of HCC.

Keywords: Hepatocellular carcinoma, Proton beam therapy, Overall survival, Local recurrence-free survival

PE-253

Clinical Outcomes of Stereotactic Body Radiation Therapy for Single Viable Hepatocellular Carcinoma at the Site of Incomplete Transarterial Chemoembolization

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Aims: Transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients may show unsatisfactory local control, with "incomplete TACE" cases having viable HCCs after multiple consecutive TACE. Moreover, no study to date has provided clear recommendation on effective local treatment option for residual viable HCC at the site of incomplete TACE. Therefore, we evaluated the clinical outcomes of patients who received stereotactic body radiation therapy (SBRT) for single viable HCC at incomplete TACE sites.

Methods: A total of 313 patients were treated with SBRT for single viable HCC after incomplete TACE between March 2012 and July 2017 at Asan Medical Center (Seoul, Korea). Incomplete TACE was defined as evidence of viable HCC at the site of TACE on follow-up images following one or more consecutive TACE procedures.

Results: The median follow-up period was 32.9 months (interquartile range [IQR], 23.6–41.4) and the median tumor size was 2.0 cm (IQR, 1.5–2.5). Almost all patients had ECOG performance status of 0 (93.3%). The median radiation dose was 45 Gy (36–60) with a median fraction size of 15 Gy (12–20). The local control rate at 3 years was 91.5%. The overall survival, out-of-field intrahepatic recurrence-free survival, and distant metastasis-free survival rates at 3 years were 72.5%, 35.8%, and 82.7%, respectively. Elevations in the level of transaminases or bilirubin of CTCAE grade ≥ 2, which may be related to SBRT without progression of intrahepatic HCC, were observed in 8 patients (2.5%). Worsening of Child-Pugh score ≥ 2 was observed in 6 patients (1.9%). No patients experienced late gastroduodenal bleeding within the radiation field.

Conclusions: SBRT showed excellent clinical outcomes in terms of local control, survival, and adverse events when used as an ablative treatment modality for residual single viable HCC at the site of incomplete TACE.

Keywords: Hepatocellular carcinoma, Incomplete transarterial chemoembolization, Stereotactic body radiation therapy

PE-254

Yttrium-90 Radioembolization Might Have Better Efficacy in Progression-Free Survival and Disease Control Rate in Patients with Hepatocellular Carcinoma Compared with Conventional Chemoembolization: A Retrospective Cohort Study

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Aims: Locoregional therapies, such as yttrium-90 (Y-90) radio-

embolization (RE) and conventional chemoembolization (CE) can effectively control localized hepatocellular carcinoma (HCC) in patients who are not amenable to curative resection. However, it has not yet been fully established which modality is more effective. The aim of this study was to compare effectiveness of RE and CE in the treatment of HCC.

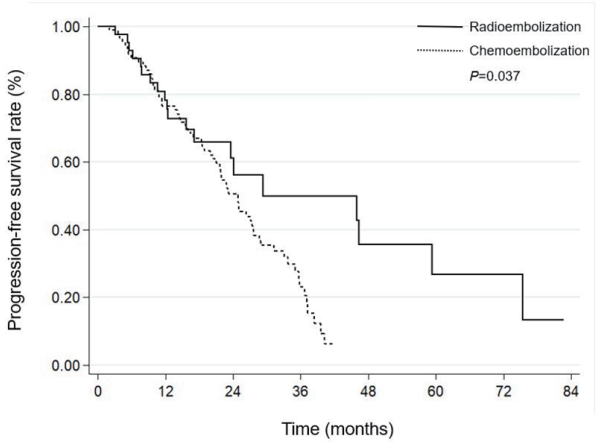

Figure 1. Comparison of and progression-free survival between patients treated with radioembolization and chemoembolization.

Table 1. Baseline characteristics

	Total (135)	RE (45)	CE (90)	*P* value
Age, median (range)	59 (35 – 81)	60 (33 – 81)	58 (35 – 84)	0.025
Sex (male)	117 (86.7%)	37 (82.2%)	80 (88.9%)	0.29
Etiology				0.83
HBV	85 (63.0%)	28 (62.2%)	57 (63.3%)	
HCV	10 (7.4%)	4 (8.9%)	6 (6.7%)	
Alcohol	11 (8.2%)	3 (6.7%)	8 (8.9%)	
NASH	2 (1.5%)	.	2 (2.2%)	
HBV + Alcohol	11 (8.2%)	.	11 (12.2%)	
HCV + Alcohol	1 (0.7%)	.	1 (1.1%)	
HBV + HCV + Alcohol	2 (1.5%)	1 (2.2%)	1 (1.1%)	
None	13 (9.6%)	9 (20.0 %)	4 (4.4%)	
Child-Pugh score				0.84
A	121 (89.6%)	40 (88.9%)	81 (90.0%)	
B	14 (10.4%)	5 (11.1%)	9 (10.0%)	
Size ≥ 5cm*	111 (82.2%)	38 (84.4%)	73 (81.1%)	0.63
Tumor extent				0.27
Unilobar	75 (55.6%)	28 (62.2%)	47 (52.2%)	
Bilobar	60 (44.4%)	17 (37.8%)	43 (47.8%)	
TNM stage				0.49
IA	4 (3.0%)	2 (4.4%)	2 (2.2%)	
IB	27 (20.0%)	12 (26.7%)	15 (16.7%)	
II	15 (11.1%)	1 (2.2%)	14 (15.6%)	
IIIA	35 (25.9%)	13 (28.9%)	22 (24.4%)	
IIIB	46 (34.1%)	14 (31.1%)	32 (35.6%)	
IVA	6 (4.4%)	2 (4.4%)	4 (4.4%)	
IVB	2 (1.5%)	1 (2.2%)	1 (1.1%)	
BCLC stage				0.07
0	1 (0.7%)	1 (2.2%)	.	
A	30 (22.2%)	14 (31.1%)	16 (17.8%)	
B	50 (37.0%)	15 (33.3%)	35 (38.9%)	
C	54 (40.0%)	15 (33.3%)	39 (43.3%)	
Okuda stage				0.48
I	110 (81.5%)	.	75 (83.3%)	
II	23 (17.0%)	35 (77.8%)	13 (14.4%)	
III	2 (1.5%)	10 (22.2%)	2 (2.2%)	
AFP ≥ 200 ng/mL	54 (40.0%)	15 (33.3%)	39 (43.3%)	0.27
Beyond Milan criteria	119 (88.2%)	38 (84.4%)	81 (90.0%)	0.35

RE, radioembolization; CE, chemoembolization

*Size of primary index tumor

Methods: A total of 135 patients who were initially treated with RE (n = 45) or CE (n = 90, age and sex matched) between March 2012 and May 2017 were reviewed retrospectively. Primary endpoints were overall survival and progression-free survival, and secondary endpoints were clinical response, the rate of down-staged HCC, and the rate of curative surgery.

Results: Of 135 patients, median age was 59 and median follow-up period was 19.1 months. There was no difference in baseline stage of HCC between treatment groups. During follow-up period, eighty-four patients (62.2%) experienced progression. There was no significant difference in overall survival between both groups after treatment (P = 0.22 by log-rank test). However, progression-free survival was higher in RE group than CE group (median, CE, 24.9 months; RE, 29.4 months; P = 0.037 by log-rank test) and RE group showed better disease control rate than CE group (55.6%, RE; 28.9%, CE; P = 0.003). In multivariable cox regression analysis, RE was in independent factor for progression (adjusted HR 0.43, 95% CI=0.22–0.84, P = 0.013). RE showed remarkably lower toxicities of all grades than CE group. Among 119 patients beyond Milan criteria, the proportion of patients who were down-staged tumor within Milan criteria were higher in the RE group than the CE group (60.5%, RE; 24.7%, CE; P = 0.025).

Table 2. Best overall response by each group.

	Radioembolization	Chemoembolization	*P* value
			0.15
Complete response	21 (46.7%)	32 (35.6%)	
Partial response	9 (20.0%)	21 (23.3%)	
Stable disease	12 (26.7%)	4 (4.4%)	
Progressive disease	3 (6.7%)	30 (33.3%)	

Table 3. Univariate and multivariable cox regression for progression-free survival

	Univariable			Multivariable*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥60	0.67	0.43–1.04	0.071			
Male	0.61	0.33–1.13	0.114			
ECOG 0 or 1	0.63	0.09–4.59	0.65			
Portal vein invasion	1.91	1.23–2.96	0.004	1.97	1.25–3.10	0.003
Y-90 RE	0.54	0.31–0.94	0.029	0.50	0.28–0.88	0.017

*Adjusted for age, sex, ECOG, and portal vein invasion

Table 4. Curative resection or liver transplantation rate

	RE	CE	*P* value
Resection	5/45 (11.1%)	4/55 (8.9%)	0.25
Liver transplantation	1/45 (2.2%)	1/55 (2.2%)	1.00
Downstaging within Milan criteria	23/38 (60.5%)	20/81 (24.7%)	<0.01

Conclusions: Radioembolization might provide better progression-free survival and might be more effective in disease control of unresectable HCC than chemoembolization. Furthermore, there are a high chance of undergoing curative surgery by down-staging and low toxicities.

Keywords: Hepatocellular carcinoma, Radioembolization, Chemoembolization, Down-staging

PE-255

Safety of Transarterial Chemoembolization in Patients with Recurrent Hepatocellular Carcinoma after Liver Transplantation

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Aims: Transarterial chemoembolization (TACE) is a widely accepted therapeutic modality for multinodular hepatocellular carcinoma (HCC). TACE is generally considered as a safe procedure even after surgical resection, but the safety data of TACE after transplantation is still lacking. The aim of this study is to investigate the safety of TACE for recurrent HCC after liver transplantation.

Methods: Medical records of 38 patients who had received living donor liver transplantation and then underwent TACE for recurrent HCC January 2001 to December 2018 were retrospectively reviewed.

Results: A total of 112 TACE procedures were performed for 38 patients, and complications were occurred in 25 patients (65%) with the incidence of 42% (48/113) per TACE procedures. Out of 112 TACE procedures performed, most frequently encountered complications were as follows: postembolization syndrome (n = 19, 17%), biloma (n = 10, 8.9%), liver abscess (n = 7, 6.2%), intrahepatic duct dilatation (n = 6, 5.4%), bacteremia (n = 2, 1.8%), hepatic artery stenosis (n = 1, 0.9%), biliary stricture (n = 1, 0.9%), and hematoma (n = 1, 0.9%). The median interval between TACE and the diagnosis of complications was 3 days (interquartile range 0-81). Most cases were managed conservatively. However, endoscopic stenting was required for intrahepatic duct obstruction (n = 2),biloma (n = 1) and liver abscess(n = 2) required endoscopic stenting or percutaneous drainage. No one died of complications. Of 24 patients who had postoperative biliary complications after transplantation, 18 patients (75%) had TACE-related complications with incidence of 42.6% (29/68) per TACE procedure, while out of the remaining 14 patients who had no postoperative complications, 7 (50%) had TACE-related complications with incidence of 28.8% (13/45) per procedure.

Conclusions: TACE is still regarded a safe procedure; however, biliary or infectious complications seem more frequently occurred in recurrent HCC following living donor liver transplantation.

Keywords: Transarterial chemoembolization (TACE), Recurrence, Hepatocellular carcinoma, Complications

PE-256

An Earlier Follow-Up Imaging Was Not Associated with Better Overall Survival after Transarterial Chemoembolization for Intermediate- or Advanced-Stage Hepatocellular Carcinoma

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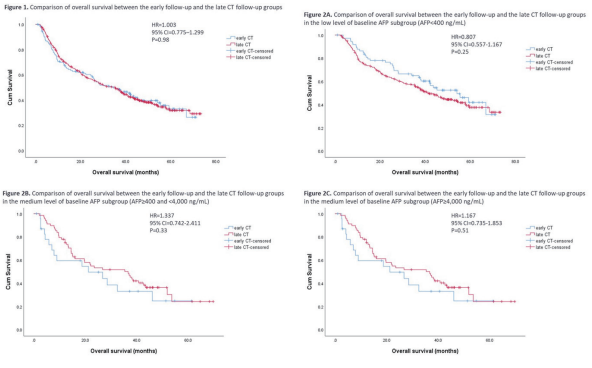
Aims: The optimal interval of follow-up imaging after transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) has not been well established. This study aimed to evaluate whether earlier follow-up imaging is associated with better overall survival (OS) among patients who underwent on-demand TACE.

Methods: This retrospective study included 519 patients who underwent superselective TACE as an initial treatment for intermediate- or advanced-stage HCC at Seoul National University Hospital between 2013 and 2015. The included patients were categorized into two groups by the interval of follow-up dynamic imaging: within 30 days (the early follow-up group, n = 133) or between 30 and days (the late follow-up group, n = 386) after TACE. The primary endpoint was OS.

Results: During follow-up (median = 26.8 months), 308 patients (59.3%) died. There was no difference in baseline age, sex, Child-Pugh score, and Barcelona-Clinic Liver Cancer (BCLC) stages between two groups. However, the mean baseline alpha-fetoprotein (AFP) level was significantly higher in the early follow-up group (25,147 *vs*. 16,058 ng/mL; *P* = 0.03). The OS was comparable between two groups (early *vs*. late follow-up: hazard ratio [HR]=1.003, 95% confidence interval [CI]=0.775–1.299; log-rank *P* = 0.98). The median OS of both early and late follow-up groups were 35.3 months (Figure 1). In a multivariable analysis, follow-up imaging interval was not independently associated with earlier death (adjusted HR=1.079, 95% CI=0.832–1.399; *P* = 0.57) after adjustment for Child-Pugh score, BCLC stage, and AFP. There was no significant difference in OS between the two groups, when sensitivity analyses were performed according to baseline AFP levels (<400; 400–4,000; and >4,000 ng/mL) with HRs ranging from 0.807 to 1.337 (all *P* > 0.2, Figures 2A–C).

Conclusions: There was no significant association between follow-up imaging interval (≤30 days *vs*. >30 days) after TACE and OS in a large-volume center with highly experienced interventional radiologists.

Keywords: Hepatocellular carcinoma, TACE, CT, Follow-up, Overall survival



PE-257

Survival Outcomes of TACE in Treatment-Naïve and Recurrent HCC after Curative Resection: A Propensity Score-Matched Analysis

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Aims: Transarterial chemoembolization (TACE) improves the survival of patients with hepatocellular carcinoma (HCC); however, TACE treatment outcomes of patients with treatment-naïve HCC (TN-HCC) and those with recurrent HCC after curative resection (R-HCC) have not yet been compared.

Methods: We recruited 448 patients with TN-HCC and 275 patients with R-HCC treated with TACE as first-line anti-cancer treatment.

Results: At first TACE, patients with TN-HCC showed a significantly lower proportion of male gender (74.9% vs. 84.3%), higher proportion of liver cirrhosis (61.9% vs. 49.3%), higher aspartate aminotransferase (median 48 vs. 31 IU/L) alanine aminotransferase (median 38 vs. 26 IU/L), alpha-fetoprotein (AFP) (median 96.6 vs. 7.7 ng/mL), and total bilirubin (mean 1.0 vs. 0.8 mg/dL) levels, longer prothrombin time (median 1.05 vs. 1.01 international normalized ratio), higher tumor number (mean 2.1 vs. 1.7), larger tumor size (median 3.1 vs. 1.6 cm), and lower proportion of Barcelona Clinic Liver Cancer stage 0-A (55.6% vs. 71.9%) than patients with R-HCC (all $P < 0.05$). Multivariate analysis showed that TACE for TN-HCC (vs. R-HCC) was an independent predictor of mortality (hazard ratio, 1.328; $P = 0.024$) with AFP level and tumor number (all $P < 0.05$). However, treatment outcomes between TN-HCC and R-HCC became statistically similar after propensity score-matched (PSM) analysis using liver cirrhosis, tumor size, and multiple tumors ($P < 0.05$).

Conclusions: Based on the similar TACE treatment outcomes observed with the PSM analysis, the current TACE treatment guideline for patients with TN-HCC might similarly be applied for patients with R-HCC.

Keywords: Hepatocellular carcinoma, Curative resection, Trans-arterial chemoembolization, Recurrence

PE-258

Establishment and Validation of a Risk Prediction Model in Patients with Hepatocellular Carcinoma Treated with Trans-Arterial Radioembolization

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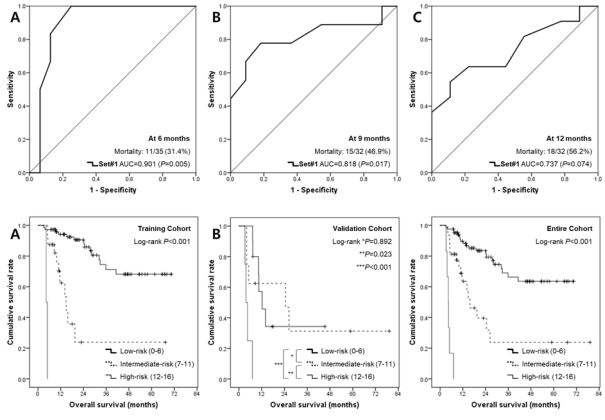
Aims: Few studies have reported the treatment outcomes of trans-arterial radioembolization (TARE) using yttrium-90 (^{90}Y) for hepatocellular carcinoma (HCC). We established and validated a new risk prediction model for patients with HCC treated with TARE.

Methods: Between 2010 and 2017, 113 and 35 patients with intrahepatic HCC treated with TARE were selected for the training and validation cohorts, respectively. The modified response evaluation criteria in solid tumors (mRECIST) were used for response evaluation.

Results: In the training cohort, the median age was 64.1 years (92 male and 19 female) and the mean survival after TARE was 50.3 months. The cumulative survival rates at six and 12 months were 92.0 and 84.0%, respectively. A new risk prediction model for patients with HCC treated with TARE (Y-scoring system) was established from the training cohort using five independent baseline variables (serum albumin <3.5 g/dL, hazard ratio [HR]=5.446; alpha-fetoprotein >200 ng/mL [HR=5.071]; tumor number ≥3 [HR=2.933]; portal vein thrombosis [HR=4.915]; and hepatic vein invasion [HR=8.500]) and two on-treatment variables (no des-gamma-carboxy prothrombin response [HR=15.346] and progressive disease at three months [HR=4.154]) for mortality (all $P < 0.05$). The predictive accuracy of the Y-scoring system was acceptable to predict six- (area under the curve [AUC]=0.845), nine- (AUC=0.868), and 12-month mortality (AUC=0.886) (all $P < 0.05$). The predictive accuracy of the system was similarly maintained in the validation cohort (AUC 0.737-0.901 at six to 12 months).

Conclusions: Our new risk prediction model can be used to stratify different prognoses in patients with HCC treated with TARE. Validation studies are required.

Keywords: Hepatocellular carcinoma, Transarterial radioembolization, Risk prediction, Survival



PE-259

Predictors of Radiological Complete Response in Patients with Intrahepatic Hepatocellular Carcinoma Treated with Transarterial Radioembolization

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Aims: Transarterial radioembolization (TARE) has shown promising results for treating hepatocellular carcinoma (HCC). We identified the independent predictors of radiological complete response (rCR) in patients with intrahepatic HCC treated with TARE.

Methods: Patients with intrahepatic HCC treated with TARE between 2011 and 2017 were recruited. The rCR was defined according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Cox-regression analysis was used to find independent predictors of rCR.

Results: The median age of the study population (83 males and 19 females) was 64.3 years. The mean survival after TARE was 55.5 months and 21 (20.6%) patients were dead during the study period. The rCR was achieved in 14 (13.7%) patients who had significantly higher serum albumin level (median 4.1 vs. 3.9 g/dL), lower total bilirubin level (median 0.6 vs. 0.7 mg/dL), lower aspartate aminotransferase level (median 30.0 vs. 43.0 IU/L), lower alkaline phosphatase level (median 79.0 vs. 103.0 IU/L), lower alpha-fetoprotein level (median 12.7 vs. 39.9 ng/mL), lower des-gamma-carboxyprothrombin level (median 575.5 vs. 2772.0 mAU/mL), lower MELD score (median 6.0 vs. 7.0), and smaller maximal tumor diameter (median 6.3 vs. 9.0 cm) than those of patients without rCR (all $P < 0.005$). Multivariate Cox-regression analysis showed that lower MELD score (hazard ratio [HR]=0.436, $P = 0.015$) and maximal tumor size < 9 cm (HR=11.180, $P = 0.020$) independently predicted the increased probability of radiological CR after TARE.

Conclusions: Low MELD score and smaller maximal tumor size were independently associated with the increased probability of rCR after TARE in patients with intrahepatic HCC.

Table. Multivariate Cox-regression analysis to identify independent predictors of radiological complete response in patients with intrahepatic hepatocellular carcinoma treated with transarterial radioembolization.

Variables	Univariate	Multivariate analysis	
	P value	*P* value	Hazard ratio (95% CI)
Serum albumin, g/dL	0.036	0.588	3.685 (0.033-415.239)
ALBI score	0.028	0.859	1.548 (0.013-189.867)
AST < 32 IU/L	0.016	0.361	1.846 (0.495-6.889)
ALP < 90 IU/L	0.042	0.573	1.526 (0.351-6.629)
MELD score	0.018	0.015	0.436 (0.224-0.849)
Maximal tumor size < 9 cm	0.015	0.020	11.180 (1.458-85.731)

ALBI, Albumin-Bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; MELD, model for end-stage liver disease; CI, confidence interval.

Keywords: Hepatocellular carcinoma, Transarterial radioembolization, MELD score, Tumor size

PE-260

Digital Subtraction Angiography Outcome during DC Bead Transarterial Chemoembolization for Hepatocellular Carcinoma

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Aims: To describe short-term outcomes after drug-eluting bead (DEB) transarterial chemoembolization in hepatocellular carcinoma (HCC).

Methods: Patients with unresectable HCC were retrospectively assigned to this study. Angiographic operators determined which feeding arteries were potentially supplying the target tumor. TACE was performed and the dosage of Doxorubicin-eluting Bead was judged by tumor size and achievement of stagnant arterial flow.

Results: A total of 118 patients, male 89.8%, female 10.2%, (mean age 60.7 ± 9.8) had a total of 176 tumor feeding arteries. The origin sites of the artery were the following: the right hepatic artery (n = 35), the left hepatic artery (n = 19), the anterior sectional artery (n = 30), the posterior sectional artery (n = 36), the segment artery (n = 41), the left gastric artery (n = 1), the gastroduodenal artery (n = 3) and the right inferior phrenic artery (n = 12). The degree of tumor feeding arteries: slight 1.7%, moderate 44.1%, serious 54.2%. The right branch portal vein thrombosis 5.9%, the left branch portal vein thrombosis 0.8%, 93.3% patients had no thrombosis. The hepatic arterioportal shunts 11.9%. After TACE, the achievement of stagnant arterial flow: complete occlusion 61.1%, near complete occlusion 34.7%, non occlusion 4.2%.

Conclusions: Digital subtraction angiography can demonstrate the type, the site and the degree of tumor feeding arteries completely and directly, thus having important value in treating HCC.

Keywords: Digital subtraction angiography, Transarterial chemoembolization, Hepatocellular carcinoma

PE-261

Curative Treatment after Transarterial Radioembolization is Associated with Better Survival Outcomes in Patients with Hepatocellular Carcinoma

Yoon Ah Kim[1], Han Ah Lee[4], Jae Seung Lee[1], Mi Young Jeon[1], Beom Kyung Kim[1-3], Young Kul Jung[4], Jun Yong Park[1-3], Ji Hoon Kim[4], Yeon Seok Seo[4], Do Young Kim[1-3], Hyung Joon Yim[4], Sang Hoon Ahn[1-3], Jong Eun Yeon[4], Kwan Soo Byun[4], Soon Ho Um[4], Kwang-Hyub Han[1-3], and Seung Up Kim[1-3]

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Background/Aims: Transarterial radioembolization (TARE) has been used to treat hepatocellular carcinoma (HCC). We identified the independent predictors of achieving subsequent curative treatments after TARE for patients with intrahepatic HCC. Also, we investigated whether the achievement of curative treatments after TARE is associated with better survival outcomes.

Methods: A total of 143 patients with intrahepatic HCC treated with TARE between 2011 and 2017 were recruited. Subsequent curative treatment was applied according to the physician's decision.

Results: The median age of the study population (115 males and 28 females) was 65.0 years. Twenty seven (18.9%) patients received curative treatments (resection in 16, transplantation in 9, and ablation in 2) after TARE, who were likely to be younger (< 65 years) (77.8% vs. 44.0%) and less likely to have hypertension (40.7% vs. 62.9%) than those who did not receive curative treatments (all $P < 0.05$). On multivariate analysis, younger age (< 65 years) (hazard ratio [HR] = 9.295, 95% confidence interval [CI] 2.859-30.221, $P < 0.001$) and AFP ≤ 200 ng/mL ([HR]=4.246, [CI] 1.294-13.935, $P = 0.017$) were independent predictors of receiving curative treatment after TARE. On multivariate analysis, curative treatment was selected as an independent predictor of mortality ([HR]=0.089, [CI] 0.011-0.721, $P = 0.023$), together with tumor burden > 50% ([HR]=5.690), portal vein thrombosis ([HR]=5.635) and progressive disease by mRECIST criteria at 3 months after TARE (all $P < 0.05$). The cumulative survival rate of patients who achieved curative treatment after TARE was significantly higher than that of patients who did not ($P < 0.001$ by log-rank test).

Table. Independent predictors of achieving curative treatment after TARE.

Baseline variables	Univariate	Multivariate		
	P value	Hazard ratio	95% CI	P value
Demographic variables				
Age < 65 years	0.003	9.295	2.859-30.221	<0.001
AFP ≤ 200 ng/mL	0.008	4.246	1.294-13.935	0.017
Multiple tumors	0.071	0.380	0.119-1.211	0.102
BCLC stage 3	0.087	0.484	0.115-2.044	0.323
Progressive disease by mRECIST criteria at 3 months	0.076	0.166	0.018-1.519	0.112

Variables are expressed as median (interquartile range) or n (%).
CI, confidence interval; TARE, trans-arterial radioembolzation; AFP, alpha-fetoprotein; BCLC, Bacrcelona Clinic Liver Cancer; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Conclusion: Younger age and AFP ≤ 200 ng/mL independently predicted the increased probability of receiving curative treatment after TARE. The achievement of curative treatment after TARE is independently associated with better overall survival in patients with unresectable HCC. Tumor burden > 50%, presence of portal vein thrombosis, and progressive disease by mRECIST criteria at 3 months after TARE are independently associated with the increased risk of mortality in patients with unresectable HCC.

Keywords: Transarterial radioembolization, Hepatocellular carcinoma, TARE, HCC

PE-262

Role and Limitation of Hepatic Arterial Infusion Chemotherapy

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Aims: The patients with advanced hepatocellular carcinoma (HCC) have a poor oncologic outcome. In this study, we evaluated role and limitation of Hepatic Arterial Infusion Chemotherapy (HAIC) in patients with advanced HCC and the efficacy of liver resection after downstaging following HAIC.

Methods: This retrospective study included 103 inoperable HCC patients with Child-Pugh class A were treated with HAIC between April 2003 to march 2015. The early response and overall response were evaluated by Modified Response Evaluation Criteria In Solid Tumors (mRECIST) and the alpha-fetoprotein (AFP) ratio. Liver resection was performed to patients who were considered to obtain a tumor-free resection.

Results: The early response was better than overall response. Response rate and disease control rate were 37 (36.3%) vs 20 (19.6%) and 83 (81.4%) vs 45 (44.1%), respectively. The median survival time (MST) in all patients was 13 months. The MST was significant different according to early response to HAIC (disease control and AFP ratio ≤1, 16 months; disease control and AFP ratio >1, 13 months; disease progression and AFP ratio ≤1, 7 months; disease progression and AFP ratio >1, 5 months; $P = 0.000$). 12 patients (11.7%) underwent liver resection following HAIC and the median survival was 37 months. Liver resection was only independent prognostic factor that associated with overall survival in multivariate analysis ($P = 0.002$).

Conclusions: HAIC could be another alternative to treat patients with advanced HCC who have preserved hepatic functional reserve. Evaluating the response to HAIC and the feasibility of operation early would provide good long-term outcomes.

PE-263

Laparoscopic Right Hepatectomy Is Feasible and Safe in Solitary Hepatocellular Carcinoma

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Background: Laparoscopic liver resection has been reported as a

safe and effective approach for the management of hepatocellular carcinoma (HCC). However, its perioperative and oncological outcomes have not been evaluated in right hepatectomy (RH) patients. Aim of present study is to compare the outcomes between laparoscopic RH (LRH) and open RH (ORH) in HCC patients.

Methods: From January 2013 to August 2017, 345 patients with HCC underwent RH. Patients with portal vein tumor thrombosis, history of preoperative locoregional therapies, multiple tumors, bile duct tumor thrombosis, the history of abdominal operation, and serosal involvement were excluded. 189 patients were selected because of Child-Pugh class A and solitary HCC.

Results: The numbers of ORH and LRH groups were 134 and 55 patients. Among LRH group, four patients (7.3%) converted open conversion due to bleeding (n = 3) and close to the tumor (n = 1). Median tumor size of ORH and LRH was 4.0 cm and 3.5 cm, respectively (P = 0.086). Preoperative factors, preoperative AFP levels, and pathologic factors were not different between the two groups. Operation time in ORH group was shorter than in the LRH group (243 min vs. 271 min; P = 0.032), but amounts of blood loss in the ORH group was more than in the LRH (300 mL vs. 200 mL; P < 0.001). Two patients in the ORH group received red blood cells transfusion, but none in the LRH group were not transfused. Ten patients in the ORH group developed postoperative complications (Clavien grade I and II), but three patients in the LRH group had postoperative complications (Clavien grade 1 and II). Median hospitalization in the ORH group was longer than in the LRH group (10 days vs. 7 days; P < 0.001). Disease-free survival (DFS) rates and patient survival (PS) rates at 1-, 2-, and 3-year were 92.1%, 89.2%, 87.4% and 95.3%, 92.4%, 90.2% in the ORH group and 100%, 94.1%, 94.1% and 100%, 100%, 100% in the LRH group, respectively. The DFS and PS in the LRH group were better than in the ORH group, but the difference did not reach significant levels.

Conclusions: LRH is feasible and safe for solitary HCC patients in experienced center. However, the oncologic outcome of LRH should be needed in further investigations.

Biliary and Pancreatic Disease

PE-264

Predicting the Choice of Operative Treatment for Common Bile Duct Diseases Complicated by Obstructive Jaundice

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Aims: The choice of operative treatment for benign and malign common bile duct diseases remains an unsolved issue. The aim of the study is to create a mathematical predictive model of choosing the operative treatment in patients with common bile duct diseases complicated by obstructive jaundice.

Methods: Based on the statistical processing of data for 118 patients who underwent surgical treatment, a mathematical model was developed for predicting the choice of biliary decompression in patients with common bile duct diseases complicated by obstructive jaundice. The patients had the following diseases: choledocholithiasis in 21 (17.8%), common bile duct strictures in 6 (5.1%), biliodigestive anastomosis strictures in 7 (5.9%), and cholangiocarcinomas of different localization in 84 (71.2%) patients. The following operative interventions were performed: percutaneous transhepatic biliary drainage (PTBD) in 88 (74.6%) cases, endoscopic in 19 (16.1%) cases, biliodigestive anastomosis or external common bile duct drainage in 4 (3.4%) cases and radical surgery without prior biliary decompression in 7 (5.9%) cases. The predictive model was developed based on the results of retrospective analysis (92 patients) and applied in patients from the prospective part of the study (26 patients).

Results: The most significant disease complication risk factors included: correct diagnosis on admission, biliary blockade level, obstructive jaundice duration, clinical diagnosis at the pre-hospital stage, Gologorsky's operation risk, presence of cholangitis, total serum bilirubin at baseline, and findings of ultrasound, fibrogastroduodenoscopy (EGD) and spiral CT. Based on the statistical data discriminant coefficients were calculated using discriminant analysis for each type of operative treatment. The designed predictive model was assessed for predictive value. For this purpose, types of interventions were selected based on initial data and factorial parameter statistics in patients from the retrospective study sample. In 89.1% of cases, the biliary decompression type was predicted correctly. The biliary decompression type in patients from the prospective part of the study was predicted correctly in 88% of cases.

Conclusions: The designed predictive model ensures a high probability and precision of choosing the operative treatment type as well as an individual approach to the pathogenetic choice.

Keywords: Choice of operative treatment, Common bile duct diseases, Obstructive jaundice, Prediction

PE-265

The Value of Serum Levels of Procalcitonin for Predicting the Severity of Acute Pancreatitis in Patients According to the 2012 Revised Atlanta Classification

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Aims: Acute pancreatitis (AP) has always been a clinical challenge. Timely assessment of severity in patients with AP is of prime importance in guiding an optimal management for these patients. Various biomarker, computerized tomography and certain scoring systems are used for assessing the severity of this disease. To evaluate serum procalcitonin (PCT), a marker of

systemic inflammation, as an effective single biomarker in determining the severity of AP.

Methods: A prospective observational study of 69 patients presenting with AP in 103 Cam Khe Clinic from May 2018 to February 2019 were included in the study. Blood samples were collected for the estimation of PCT on day of admission. Chemiluminescent immunoassay (Elecsy Brahms PCT Roche Diagnostic) was used for measuring serum PCT concentration. The Revised Atlanta classification was used as the gold standard to stratify severity of AP. The predictive accuracy of PCT was measured as the area under the receiver operating characteristic curve (AUC).

Results: Female accounted for 55.2%. Mean age was 48 years (from 35 to 68). Severe AP with organ failure, moderate AP and mild AP accounted for 12.6%, 15.4% and 72% respectively. Causes of AP such as gall stone: 46,8%, alcoholic: 20,6%. Mean ± SD value of serum PCT for mild, moderate and severe AP on day of admission were 0.5 ± 1.23 ng/ml, 1.58 ± 1.36 ng/ml and 3.2 ± 4.3 ng/ml respectively. The cut off value of serum PCT was 0.5 ng/ml between mild and moderate AP (AUC = 0.81, 95% CI = 0.683 - 0.853, sensitivity: 71%, specificity: 86.5%). The cut off value of serum PCT was 0.61 ng/ml between moderate and severe AP (AUC = 0.76, 95% CI = 0.628 - 0.91, sensitivity: 79.3%, specificity: 62.1%).

Conclusions: Procalcitonin is a practical, simple parameter that can be used in order to diagnose severe acute pancreatitis earlier and to monitor the clinical prognosis of the disease.

Keywords: Acute pancreatitis, Procalcitonin, Prognosis, Severity

PE-266

Statins Use Is Associated with Reduced Risk of Cholangiocarcinoma: A Systematic Review and Meta-Analysis

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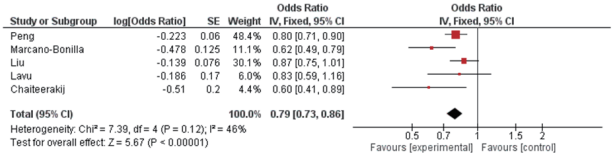
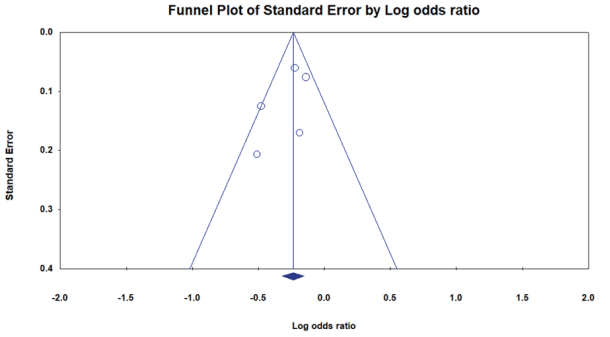
Aims: Statins are widely used for primary and secondary prevention of cardiovascular disease. Preclinical studies have shown that statins have anticancer properties. Epidemiological studies have shown that the use of statins is associated with reduced risk of various cancers and cancer related morbidity/mortality. We conducted a meta-analysis of all available studies to investigate the association between the use of statins and the risk of developing cholangiocarcinoma (CCA), which, to our knowledge, is the first meta-analysis on this matter.

Methods: A comprehensive literature search for articles and abstracts published from January 2000 to December 2018 was carried out. Studies that had strictly reported Odds Ratio (OR), Relative Risk (RR), or Hazard Ratio (HR), with 95% confidence interval (CI) were included in the study. Pooled adjusted ORs with corresponding 95% CIs were calculated using fixed effects model.

Results: Five observational studies were included in our analysis, with 8,450 CCA subjects and 978,008 healthy controls. Administration of statins significantly reduced the incidence of CCA (OR = 0.79, 95% CI: 0.73-0.86, $P < 0.0001$). No heterogeneity was found in the study ($I^2 = 46\%$, $P = 0.12$). No evidence of publication bias was observed in this meta-analysis.





Conclusions: Our study shows statistically significant association between the use of statins and 0.79-fold decreased risk of CCA.

Keywords: Statins, Cholangiocarcinoma

PE-267

Molecular Characteristics Associated with 18F-FDG Uptake in Intrahepatic Cholangiocarcinoma

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Aims: In intrahepatic cholangiocarcinoma (iCCA), genetic characteristics on ^{18}F-FDG-PET scans are not yet clarified. If they are evaluated, we can predict molecular features based on the FDG uptake. We analyzed RNA sequencing in iCCA patients to evaluate gene expression signatures associated with FDG uptake patterns.

Methods: We performed RNA sequencing of 22 cases iCCA who underwent preoperative ^{18}F-FDG- PET, and analyzed the clinical and molecular features according to the maximum standard uptake value(SUVmax). Genes and biological pathway which are associated with SUVmax were analyzed.

Results: Patients with SUVmax higher than 9.0(n = 9) had poorer disease-free survival than those with lower SUVmax(n = 13, $P = 0.035$). Genes related to glycolysis and gluconeogenesis, phosphorylation and cell cycle were significantly correlated with SUVmax ($| r | \geq 0.5$). RRM2, which is related to the toxicity of Gemcitabin was positively correlated with SUVmax, and

SLC27A2 which is associated with Cisplastin response was negatively correlated with SUVmax. Cell cycle, hypoxia and metabolism-related pathways were enriched in high SUVmax patients.
Conclusions: The genomic features of gene expression and pathways can be predicted by FDG uptake features in iCCA. Patients with high FDG uptake have enriched cell cycle, metabolism and hypoxic pathways, which may lead to a more rational targeted treatment approach.
Keywords: Cholangiocarcinoma, FDG, Gene expression

PE-268

Risk Factors Associated with Locoregional Failure and Estimation of Survival after Curative Resection for Patients with Distal Bile Duct Cancer

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Aims: Our aim was to identify the risk factors associated with locoregional recurrence in resected distal bile duct cancer (DBDC), and to determine the subgroup that may benefit from adjuvant radiotherapy.
Methods: Between 2001 and 2013, we retrospectively analyzed 93 patients with DBDC who had undergone curative resection. Patients who received adjuvant radiotherapy were excluded. The primary outcome was the 3-year LRFFS in patients undergoing surgical resection for distal bile duct cancer; the secondary outcomes were OS and patterns of failure.
Results: The 3-year locoregional failure-free survival (LRFFS) and overall survival (OS) rates for all patients were 50.7%, and 53.2%, respectively. On multivariate analysis, the preoperative carcinoembryonic antigen (CEA) level, resection margin, histologic grade, T stage, and N stage were significant prognostic factors for LRFFS. Locoregional recurrence was observed in more than 78% of the patients who underwent R1 resection and were node-positive, and the 3-year LRFFS rate was 19.3%. The 3-year LRFFS rate was 46.9% in the patients who underwent R0 resection and was node-negative with more than 2 risk factors (preoperative CEA level ≥ 5 ng/mL, poorly differentiated histologic grade, and T3 stage). On multivariate analysis for OS, patients with more than 2 risk factors showed a 7-fold higher risk of death, compared with patients with 1 or no risk factor. The important risk factors of locoregional failure in patients with DBDC who underwent resection were R1 resection and positive lymph nodes.
Conclusions: Adjuvant radiotherapy should be considered for these patients to improve oncologic outcomes. Patients undergoing selective R0 resection and those with node-negative status and multiple locoregional failure risk factors may benefit from adjuvant radiotherapy.
Keywords: Distal bile duct cancer, Locoregional failure, Curative resection

PE-269

Beneficial Effects of Cassia Angustifolia (Senna Leaves) Treatment Improves Constipation, Liver Functions and Defense of Red Blood Cells in Type 2 Diabetic Patients

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Aims: Diabetes has been reported with constipation leading to the development of diabetic complications in spite of controlling the blood glucose levels by antidiabetic drugs. Our objective was to investigate effects of Cassia angustifolia (Senna leaves) extract on constipation, liver dysfunctions and defence of red blood cells in type 2 diabetic patients.
Methods: A total number of 100 subjects were selected with the age ranging from 45 to 60 years. Among them, 50 diagnosed type 2 diabetes individuals were included in the Group A and 50 apparently healthy individuals were selected as Group B for comparison. Cassia angustifolia (Senna leaves extract) was prepared in hot water and orally administered to type 2 diabetic patients with constipation. This treatment was thrice a week in 1 st month, twice in a week in corresponding 2 nd and 3 rd months and once in a week from 4 th to 6 th months. The defensive enzyme, the glutathione peroxidase, sodium dismutase and catalase were measured in the red blood cells along with the levels of reduced glutathione. The liver function test was performed by measuring hepatic enzymes aminotransferases (Aspartate amino transferase (ASAT) activity, alanine amino transferase (ALAT)) and lipid profile levels.
Results: The present study showed that higher levels of serum hepatic enzymes in diabetic patients. The diabetic patients were found to be high blood glucose levels and altered lipid profile with vulnerable to skin infection particularly in the pelvic regions, backside, legs, etc. which were reversed to normal after six months of Senna leaves treatments. The neurological disorder like sustaining pain in legs was also recovered with the treatment. The stools quality also changed to normal. The glutathione peroxidase decreased in red blood cells of diabetics by 20-30%, normalized after six months of treatment with Senna leaves extract. The reduced glutathione found to be decreased in diabetics by 15-20%, normalised. There was also normalize enzymes activity of aminotransferases with treatment to diabetic patients.
Conclusions: Senna leaves extract treatment to diabetic patients not only normalize the defense of red blood cells but also corrects skin infection, liver disorder, neurological disorder and physiological disorder.

Keywords: Diabetes patients, Cassia angustifolia (Senna leaves extract), Serum hepatic enzymes, Liver disorder, Constipation

PE-270

Comparison of Surgical Outcomes of Robotic and Laparoscopic Pancreaticojejunostomy after Pancreaticoduodenectomy in Patient with a Soft Pancreas: Multi-Institutional Study

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Aims: A soft pancreas remains a potent risk factor of postoperative pancreatic fistula following pancreaticoduodenectomy (PD). Recently, minimally invasive PDs have been gradually expanding its application. This study aims to evaluate the effect of anastomotic technique of robotic versus laparoscopic pancreaticojejunostomy (PJ) on postoperatic pancreatic fistula formation among patients with soft pancreas in multi-institutional database.

Methods: From January 2014 to January 2019, 147 patients with soft pancreas and small pancreatic duct less than 3 mm diameter, who underwent minimally invasive PD for periampullary pathologies, were identified. Surgical outcomes of 97 patients who underwent laparoscopic PJ and 50 patients who underwent robotic PJ were compared.

Results: General demographics were comparable between laparoscopic and robotic group, except patients with higher ASA score were more included in laparoscopic group. Majority of indications were common bile duct cancer and ampullary cancer in both laparoscopic and robotic group (61.8% vs. 60%, P = 0.166). All patients underwent duct-to-mucosa anastomosis for pancreaticojejunostomy. Mean pancreatic duct size was also comparable (1.98±0.69 vs. 2.08±0.96, P = 0.475) Mean operative time and estimated blood loss were similar. Total postoperative pancreatic fistula rate (57.7% vs. 46.0%) and Clinically significant fistula rates higher than grade B (11.3% vs. 14.0%) were not statistically different (P = 0.279). Delayed gastric emptying was more often in laparoscopic group (7.2% vs. 0%, P = 0.239) without statistical significance. Total postoperative complications (30.9% vs. 38.0%) and severe complications higher than grade III (4.1% vs. 18.0%) were more frequent in robotic group (P = 0.024). Length of hospital stay was comparable.

Conclusions: Our study showed similar postoperative pancreatic fistula rate in both surgical modality. However, robotic approach demonstrated higher postoperative complication rate.

Keywords: Robot, Laparoscopy, Pancreaticojejunostomy, Soft pancreas

PE-271

Mucinous Cholangiocarcinoma with Hemobilia: A Case Report

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Aims: Pure mucinous cholangiocarcinoma is a very rare variant of intrahepatic cholangiocarcinoma.

Methods: An 83-year-old female was presented to our hospital with an epigastric pain. She had no liver disease. Contrast-enhanced abdominal computed tomography showed a dilatation of left hepatic duct containing both irregularly nodular enhancing components and hematomas. Endoscopic retrograde cholangiogram revealed a hemobilia of common bile duct. We initially diagnosed as an intraductal papillary neoplasm of the bile duct with hemobilia. Both left hemihepatectomy including middle hepatic vein and caudate resection was performed.

Results: Pathologic examination reported mucinous adenocarcinoma with directly invades into hepatic parenchyma and beyond the wall of bile duct. She was discharged without complication on postoperative day 9 and had no recurrence for 6 months.

Conclusions: Herein, we described a rare case of mucinous cholangiocarcinoma with hemobilia.

PE-272

Gallbladder Paraganglioma with Hemorrhage: A Case Report

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Aims: Gallbladder paraganglioma is a very rare tumor and only a few cases have been reported so far.Most of these tumors are asymptomatic and confirmed incidentally after operation. The clinical significance of gallbladder paraganglioma is differential diagnosis with gallbladder cancer or other gallbladder tumor.

Methods: A 48-year-old woman presenting with intermittent abdominal pain. The laboratory tests were all within normal range including tumor marker. MRI showed 8 cm sizedmass lesion in gallbladder body and fundus with low signal intensity in T2-weighted imagesconsidered as hemorrhage.We planned a laparoscopic cholecystectomy under the impression of gallbladder tumor with hemorrhage.

Results: We performed laparoscopic cholecystectomy successfully.In the gallbladder lumen, several black stonesless than 1 cm in diameterand large hematomawere observed. And about 1 cm sized polypoid lesion was detected in the fundus. In microscopic examination of polypoid lesion showed cuboidal cells including granular cytoplasm surrounded by a fibrous septum containing blood vessels.The chief cell was nested in the inside and the spindle shape sustentacular cells surrounded by the

Zellballen cellular arrangement. Synaptophysin, CD56, chromogranin staining were strongly positive for chief cells. In the histopathologic examinations, the diagnosis was gallbladder paraganglioma with hemorrhage.
Conclusions: Gallbladder paraganglioma is extremely rare tumor and usually diagnosed incidentally after operation. We need to aware of this disease entity for differentiation of this tumor with other gallbladder tumors.

PE-273

Clinical Outcomes of Robotic Cholecystectomy: Single Center Early Experience

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Aims: Laparoscopic cholecystectomy is the gold-standard approach for gallbladder diseases. Recently, the robotic platform including single port has been released, which could technically facilitate cholecystectomy. Therefore, we report our early experience in robotic cholecystectomy at Chonbuk national medical center.
Methods: From September 2017 to November 2018, all consecutive patients(n = 72) who underwent robotic cholecystectomy were retrospectively analyzed. Variables of interest for this study were patient demographics, operative times for the procedure and morbidities.
Results: Among 72 patients, the mean age was 43.4 years with range of 15-68 years. The male (n = 26) to female (n = 46) ratio was 1:1.8. The indication of cholecystectomy were stone in 57 cases and polyp in 15 cases. Single incision and 3-port robotic cholecystectomy were performed 59 and 13 cases, respectively. The mean docking and operating times were 8.6 and 83 mins. Total numbers of open or laparoscopic conversion are 2 cases due to sever adhesion. Postoperative complication was shown cholangitis in 1 case. (Clavien-Dindo classification grade 2)
Conclusions: In our results, robotic cholecystectomy was shown feasible and safe procedures.

PE-274

Differentiation of the Gallbladder Adenomyomatosis from Early-Stage Gallbladder Cancer before Surgery

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Aims: This study compared perioperative and clinical outcomes in patients undergoing laparoscopic cholecystectomy for gallbladder adenomyomatosis (GBA) or early-stage gallbladder cancer (GBC).
Methods: Among the patients who underwent laparoscopic cholecystectomy from January 2011 to December 2017 in our institution, 194 patients histopathologically diagnosed with GBA and 30 patients with GBC were enrolled in this study. Their perioperative and clinical outcomes were compared.
Results: There were no significant differences in sex (1.0:0.8 vs. 1.0:0.7, male:female, $P = 0.734$), BMI (23.9 ± 3.4 vs. 24.0 ± 3.8 kg/m^2, $P = 0.916$), or preoperative liver function tests between the GBA and GBC groups. The GBC group was significantly older (50.5 ± 14.1 vs. 65.9 ± 10.6 years, $P < 0.001$) and had higher ASA grade (40.3 vs. 63.4, grade II or III (%), $P = 0.043$) than the GBA group. Although there was no significant difference in preoperative diagnostic methods ($P = 0.442$), the GBC group showed significantly higher rate of misdiagnosis on preoperative imaging work-up, compared with postoperative histopathologic findings (30.9% vs. 53.3%, $P = 0.011$). Patients with gallstones in the GBA group were significantly more than those in the GBC group (68.6% vs. 40.0%, $P = 0.004$).
Conclusions: This study revealed the difficulty of accurate diagnosis of early-stage GBC. If an older patient who was hospitalized for biliary colic does not have any gallstones but thickened gallbladder wall with inflammation on preoperative diagnostic exam, the possibility of early-stage GBC as well as benign diseases such as acute / chronic cholecystitis and GBA should be considered.

PE-275

Management of Xanthogranulomatous Cholecystitis Combined Wth Common Bile Duct Adenoma Mimicking Biliary Malignancy of Old Age Patient: A Case Report

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Aims: Xanthogranulomatous cholecystitis is an unusual variant of chronic cholecystitis with infilarative inflammatory condition. and it is not easy to distinguish this disease entity from gallbladder malignancy on radiologic findings. Therefore, there are a lot of concerns about determination of treatment methods preoperatively. We present a case report of an unusual case of Xanthogranulomatous cholecystitis accompanied by bile duct tumor of old age with multiple comorbidity.
Methods: The patient was a 81-year-old male and he was underwent general weakness with nausea and vomiting for several days. There was right upper quadrant tenderness without fever on physical examination. There was multiple comorbidity include diabetes melitus, hypertension, reflux esophagitis and hiatal hernia on past history. Serum laboratory findings showed mild anemia, creatinie 1.42 mg/dl, alkaline phosphatase 590 IU/L, r-GTP 89IU/L and normal liver enzyme. Serum total bilirubin level was 0.4mg/dl. CA 19-9 was 714.90U/mL. Abdomen CT showed gangrenous cholecystitis with a small stone in cystic duct and perforation of GB wall with pericholecystic abscess and edematous hepatoduodenal ligament. PET CT showed

probably common hepatic duct malignancy with extrahepatic biliary obstruction. we performed cholecystectomy, CBD resection and hepaticojejunostomy. There was no malignant tissue in bile duct and gallbladder on intraoperative frozen section.
Results: There was no intraoperative complication. Pathologic report was xanthogranulomatous cholecystitis and bile duct adenoma. Postoperative course was uneventful.
Conclusions: We reported a case of xanthogranulomatous cholecystitis with biliary adenoma mimicking biliary malignancy. It needs active efforts to make a precise diagnosis and treatment, Even in old aged patient with multiple comorbidity.

PE-276

Laparoscopic Resection of Schwannoma in the Pancreas

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Aims: Pancreatic schwannomas are very rare neoplasm that arise from Schwann cells. They can be misdiagnosed as another pancreatic tumor. Although they are rare, they must be considered during the differential diagnoses of cystic pancreatic masses. We experienced a pancreatic schwannoma case.
Methods: A 60-year-old female with back pain was transfered to our hospital. CT showed a homogenous low density mass containing solid and cystic portion with a smooth margin with a clear border of 3.5 x 4 cm size in the pancreas body.
Results: Laparoscopic pancreatic tumor resection was performed. The tumor was histologically diagnosed as schwannoma. Immunohistochemically, the tumor was positive for S-100 protein and negative for C-kit, CD-34, smooth muscle actin.
Conclusions: Pancreatic schwannoma can be adequately treated with laparoscopic enucleation when suspected during exploration.

PE-277

Synchronic Ampullary Neuroendocrine Tumor and Extra-Gastrointestinal Stromal Tumor in Association with Neurofibromatosis Type 1: A Case Report

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Aims: The coexistence of synchronic gastrointestinal stromal tumor (GIST) and neuroendocrine tumor (NET) in a patient with neurofibromatosis type 1 (NF1) is extremely rare, and furthermore report of combined extra-gastrointestinal stromal tumor (E-GIST) and NET in NF-1 patient was not described yet, in the literature. Here, we report two discrete synchronous neoplasms in a patient with NF-1.
Methods: A 80-year-old lady presented with general weakness and dizziness. She had a medical history of perforated acute cholecystitis and peritonitis managed with percutaneous cholecystostomy, 2 years ago. Physical examination revealed icterus skin color and multiple neurofibromas all over the body. Before her visiting our hospital, abdomen CT scan was done at local clinic and CT showed dilated both intra- and extrahepatic bile ducts and hypervascular mass around 2nd portion of duodenum. Laboratory test revealed no specific abnormal findings. Endoscopy was performed and it showed an ampullary mass lesion with ulceration which was biopsied but other mass around duodenal 2nd portion wasn't discovered. Histopathologic result was reported neuroendocrine tumor of ampulla of Vater with histologic grade 1.
Results: The patient underwent open laparotomy, cholecystectomy and transduodenal ampullectomy with retroperitoneal mass excision placed at the retroperitoneum, behind posterior wall of duodenum in view of CT findings. On microscopic section and immunohistochemistry, ampullary mass reported NET, grade 1 as same as previous endoscopic biopsy and retroperitoneal mass, behind the duodenal 2nd portion was turned out GIST, very low risk.
Conclusions: Herein, we report a extramly rare case of synchronous E-GIST and NET with a history of neurofibromatosis type 1

PE-278

Benefits and Pitfalls of Surgical Resection after Downstaging Concurrent Chemoradiation Therapy in Patients with Locally Advanced Perihilar Cholangiocarcinoma

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Aims: Although surgical complete resection is only curable chance of long-term survival, majority of patients who present with perihilar cholangiocarcinoma (PHCC) are unresectable at the time of diagnosis. This study evaluated the down-staging efficacy and postoperative outcome of neoadjuvant concurrent chemoradiation therapy (NACCRT) followed by surgical resection in patients with locally advanced PHCC.
Methods: From January 2000 to December 2018, 326 patients underwent surgical resection for treatment of PHCC at Severance Hospital. Among these patients, 28 (8.6%) patients got CCRT due to locally advanced extent of tumor. Perioperative outcome of the patients with NACCRT was compared the patients without neoadjuvant CCRT. Additionally, long-term survivals after surgical resection were evaluated and analyzed.
Results: Of the 28 patients underwent NACCRT, 71.4% were due to involvement of main hepatic artery or portal vein. R0 resection was achieved for 26 (92.9%) including 5 patients with complete pathological response. This curability rate is significantly higher compared with non-CCRT group. (73.5%, $P = 0.023$) Hospital mortality (25% vs 6.7%) was significantly higher in CCRT group ($P = 0.001$). NACCRT group showed a

high frequency of complication (78.6% vs 61.7%) even though there was no statistically significance (P = 0.083). Disease free survival and overall survival were not significantly different between two groups (P = 0.939 and P = 0.575, respectively).
Conclusions: NACCRT does not affect long-term survival. However, NACCRT could contribute to allow tumor downstaging and has potential to increase resection rate and curability in patients with locally advanced PHCC. High mortality and complication rates should not be overlooked. Optimal treatment protocol should be developed in a well-designed prospective study.

PE-279

Surgical Outcomes of Bismuth Type IV Perihilar Cholangiocarcinoma

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Aims: Perihilar cholangiocarcinoma (PHCC) Bismuth type IV tumors is generally regarded as unresectable owing to tumor location where extends into secondary biliary radicals on both side of the liver. With optimized preoperative management and advancement of surgical techniques, aggressive surgical resection has been applied in patients with Bismuth type IV, but still challenging. In this study, we introduced our experience on surgical resection in patients with Bismuth type IV.
Methods: Between January 2000 and December 2018, 325 consecutive patients with perihilar cholangiocarcinoma underwent surgical resection at Severance Hospital, Korea. Among them, 81 patients (24.9%) present Bismuth type IV PHCC. Short term and long-term surgical outcomes were analyzed between Bismuth type IV and other types.
Results: Of the 81 patients with type IV PCCA, right sided hepatectomy was the most common procedure (44 patients) (right hepatectomy, left hepatectomy, right trisectionectomy, central bisectionectomy). R0 resection rate was 59 patients (72%). Complications of Clavien-Dindo grade III or more occurred in 43 patients (53.0%) and 11 (13.6%) died from 90 days hospital mortality. Total Complication rate was significantly higher in type IV than other type of tumors. (63.8% vs 46%, P = 0.006). Disease free survival and overall survival were not significantly different between type IV PHCC and other type. (P = 0.592 and P = 0.328, respectively) In multivariate analysis, R0 resection was only significant prognostic factor for long-term survival. (P = 0.001).
Conclusions: Although resection for type IV PHCC is technically challenging with high complication rate, aggressive tumor resection to achieve R0 resection should be considered as a first treatment to provide long-term survival.

PE-280

Minimally Invasive Interventions in Patients with Mechanical Jaundice

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Aims: The results of 23 patients with mechanical jaundice syndrome who underwent percutaneous cholangiostomy were analyzed.
Methods: In the Department of surgery of the regional medical center of Kyzylorda in 2017, 23 patients received with mechanical jaundice syndrome had percutaneous cholangiostomy. Of these, cancer of the pancreatic head – 11 (47,8%), cancer of the large duodenal papilla of the duodenum in 5 (21,7%), choledocholithiasis – 4 (17,3%), cancer Klatskin – 3 (13.0 per cent). The age of patients from 55 years to 76 years. Of these, 9 men (39.1%), 14 women (60.8%). The level of total bilirubin ≥ 380,0 mmol/L.
Results: After complete examination of patients, performed preventive antibiotic therapy. Under angiographic installation in the operating unit, under local anesthesia, a puncture is performed inside the hepatic bile ducts under ultrasound control in Doppler mode. Further aspires stagnant bile, a Guidewire is 0.38. According to the method of the Seldinger bile ducts biroute to 10 Fr. Then, under the control of intraoperative cholangiographies sets hydrophilic Pigtail catheter 8 Fr. Further drainage is fixed on the skin. In the early postoperative period, the cholangiostomy tube is washed with 5 ml 0.9% sodium chloride solution several times a day. In office patients receive analgesics, medications, infusion terapia, according to testimony carried zamorojennoi infusion of fresh plasma, plasmapheresis fractional. 15-25 days after surgery the level of total bilirubin is reduced to 40,0-60,0 mmol/l. Then it is possible to conduct radical surgery. The average duration of treatment was 11.5 days. There was no mortality.
Conclusions: Percutaneous cholangiostomy under ultrasound control is a promising direction of biliary decompression
Keywords: Minimally invasive, Interventions, Mechanical, Jaundice

PE-281

Minimally Invasive Endoscopic Technologies in Complex Treatment of Patients with Obstructive Jaundice Syndrome

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Aims: The aim of the study was to assess the possibility of endoscopic methods of decompression of the biliary system in optimizing the treatment of patients with obstructive jaundice.
Methods: The analysis of the results of treatment of 587 pa-

tients with obstructive jaundice of various etiologies for the period from 2010 to 2017 was conducted at the clinic of West Kazakhstan Marat Ospanov state medical university. Obstructive jaundice of benign genesis in 541 (92.2%), malignant genesis in 46 (7.8%) patients. Endoscopic retrograde cholangiopancreatography (ERCP) was performed, resulting in 369 (62.8%) cases of choledocholithiasis (including after cholecystectomy - in 202), stenosis of the major duodenal papilla - in 140 (23.9%), terminal choledochal stricture - in 59 (10.1%), a tumor of the pancreatic head - in 12 (2.0%), Klatkin's tumor - in 3 (0.5%) and a stricture of the hepaticocholedochus after laparoscopic cholecystectomy - in 4 (0.7%). Concomitant diseases were observed in 72.1%.

Results: In order to decompress the bile ducts, endoscopic papillosphincterotomy (EPST) was performed in 187 (31.8%) patients, EPST with choledocholithoextraction - 320 (54.5%) patients, 23 of them underwent mechanical lithotripsy with subsequent extraction of concrements, EPST and endoprosthetics - in 75 (12.7%), and nasobiliary drainage - in 5 (0.8%). In 4 patients litoextraction after EPST was not successful. Frequency of complications was 13,6% (80 cases), in the structure: acute pancreatitis - in 65 (11%); duodenal bleeding in 12 (2%); in 3 patients perforation of the back wall of the intestine was registered (in 1 (0,2%) case death was registered).

Conclusions: Minimally invasive endoscopic decompression interventions are effective for biliary obstruction, allowing for routine surgical interventions in the most favorable conditions, and can serve as an alternative to surgical treatment in elderly patients with severe concomitant pathology.

Keywords: Biliary system, Choledocholithiasis, Obstructive jaundice, Endoscopic interventions

PE-282

The Efficacy of Single-Stage Endoscopic Treatment of Complicated Forms of Cholelithiasis

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Aims: The aim of our study was to evaluate the efficacy and safety of a single-stage endoscopic treatment of cholelithiasis complicated by choledocholithiasis and mild severity of obstructive jaundice.

Methods: A prospective cohort study of patients diagnosed of cholelithiasis complicated by choledocholithiasis and mild severity of obstructive jaundice (according to the classification of V.D. Fedorov et al. 2000), who were treated with the single-stage treatment a single-stage treatment - laparoscopic cholecystectomy and intraoperative endoscopic retrograde cholangiopancreatography, endoscopic papillosphincterotomy with endoscopic mechanical lithoextraction of calculi and laparoscopic cholecystectomy, laparoscopic choledocholithotomy, drainage of the common bile duct in hospital surgery clinic of West Kazakhstan Marat Ospanov state medical university for the period from 2014 to 2018. The primary outcomes were complications, hospital stay, operative time and timing of cholestasis resolution.

Results: The study included 35 patients. All patients underwent laparoscopic cholecystectomy. Intraoperative endoscopic retrograde cholangiopancreatography, endoscopic papillosphincterotomy with endoscopic mechanical lithoextraction of calculi performed in 24 (68.6%), 11 (31.4%) - laparoscopic cholecystectomy, laparoscopic choledocholithotomy, drainage of the common bile duct. Normalization of biochemical parameters characterizing cholestasis (bilirubin, alkaline phosphatase) and cytolysis (AsAT and AlAT) within 3 days after single-stage treatment was observed in 31 patients (88%). Mean operative time was 102.6 ± 34.2 minutes. Mean hospitalization stay was 6.8 ± 1.5 days. Complications directly related to the operation were found in 2 patients (5.7%): acute pancreatitis was observed, accompanied by increased levels of blood amylase and leukocytosis. Comprehensive conservative therapy in these patients had a positive clinical result. Deaths were not recorded.

Conclusions: This study demonstrated that single-stage endoscopic treatment may be effective and safe for cholelithiasis complicated by choledocholithiasis and mild severity of obstructive jaundice.

Keywords: Single-stage, Endoscopic treatment, Cholelithiasis, Obstructive jaundice

PE-283

Rare Experience of Complication of a Spilled Gallstone after Laparoscopic Cholecystectomy: Case-Report

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Aims: Laparoscopic cholecystectomy is the gold standard for gallstone disease and worldwide procedure. The spillage of gallstones, rarely makes late complication but may cause major complications.

Methods: Retrospective review of medical records was performed for the patient who had suffered from a spilled stone.

Results: A 46-year-old man came to my center for right flank pain. He checked abdominal Computed tomography (CT) in local clinic, the clinic doctor accessed to liver abscess and referred to my center. First my clinic hepatologist check abdomen sonography for the abscess aspiration. The radiologist found a big stone in abscess poket. He did laparoscopic cholecystectomy 2 years ago. The cause of his abdominal pain was fluid collection around stone. I decided to operate for remove the stone. We did laparoscpic exploration, removed abscess and found a big gallstone (18 mm). The patient was discharged on the 3rd post-operative day. We followed up abdominal CT on 24th post-operative days and Perihepatic fluid collection was decreased and the patient is free from abdominal pain.

Conclusions: When we do laparoscopic cholecystectomy, we

must try to avoid gallbladder perforation and try to minimize spillage of gallstones.

PE-284

Iatrogenic Bile Duct Injury Associated with Anomalies of Isolated Right Anterior Segmental Hepatic Duct Injury Following Laparoscopic Cholecystectomy: A Rare Case Report

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Aims: Bile duct injuries remain one of the most devastating complications of both open and laparoscopic cholecystectomy(LC). Bile duct injury with LC has often been attributed to surgical inexperience, but it is also clear that aberrant bile ducts are present in a significant number of patients who sustain biliary injuries during these procedures.
Methods: We presented a patient with iatrogenic bile duct Injury associated with anomalies of isolated right anterior segmental hepatic duct Injury following laparoscopic cholecystectomy.
Results: (CASE REPORT) The anormaly of the right anterior hepatic duct was unexpectedly identified in an old woman following laparoscopic cholecystectomy. Anormalies of Bile duct located in the right anterior hepatic duct to cystic duct. This duct was 3mm sized and clipped. Patient had a bile duct injury and subsequent bile leak. Treatments included endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous drainage for 2 months. The patient was treated successfully by nonsurgical procedures after 2 months.
Conclusions: This unusual anatomical variation of the biliary tract is mainly discovered during the operation. Thus, surgical injury of these ducts is inevitable and it provokes the severe complication of bile leak. Anormaly of bile ducts are associated with a high risk of surgical bile duct injury. Meticulous operative technique combined with surgeons' awareness concerning this peculiar anatomical aberration leads to a safe laparoscopic cholecystectomy. Successful management requires adequate identification of the lesion, and multidisciplinary treatment is necessary. Some of patients could be treated successfully by nonsurgical procedures.

PE-285

PD-L1 Expression in Extrahepatic Biliary Tract Cancers: A Comparative Study Using 22C3, SP263 and E1L3N Anti-PD-L1 Antibodies

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Aims: Treatment with monoclonal antibody to programmed cell death protein 1 (PD-1) has showed promising results in patients with programmed cell death ligand-1 (PD-L1)-positive advanced biliary tract cancer. In an ongoing clinical trial of pembrolizumab on biliary tract cancer, 22C3 assay is being used for PD-L1 evaluation. The frequency of PD-L1 positivity varies in bile duct cancers, which may be due in part to the assay used.
Methods: We evaluated PD-L1 expression in 183 extrahepatic bile duct cancers, including 89 perihilar and 94 distal bile duct cancers, using 22C3, SP263 and E1L3N antibodies.
Results: Using 22C3 antibody, tumoral PD-L1 was expressed in 16.9% at a 1% threshold. Using the SP263 and E1L3N, the tumoral PD-L1 positivity was 26% and 7.1%, respectively. In evaluation of whole tissue sections, 59.6% of PD-L1 positive cases exhibited low percentage (<10%) of positive tumor cells. Tumoral PD-L1 positivity was associated with histologic differentiation (P = 0.017) and mucin phenotype (P = 0.041). Although there was no statistically significant association between clinical outcome and tumoral PD-L1 expression at 1% cut-off, PD-L1 expression ≥10% was associated with worse overall survivals and disease-free survivals (SP263 OS: P = 0.012, DFS: P = 0.042).
Conclusions: By 22C3 assay, tumoral PD-L1 was expressed in 16.9% at a 1% threshold. The SP263 assay showed the highest PD-L1 positivity both on tumor cells and immune cells, followed by 22C3 and E1L3N assay. High PD-L1 expression (≥10%) was associated with poor prognosis in extrahepatic bile duct cancer patients.
Keywords: Cholangiocarcinoma, Bile duct cancer, PD-L1, Immunohistochemistry

PE-286

ELCC

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Aims: Gallbladder stones – is one of the worldwide disease, which occurs in 10% of the population in the world. And 97-98% of cholecystectomies perfume by the laparoscopic method. According to many reports after laparoscopic cholecystectomy (LCE) complications observed at 1% to 8,5%. The aim is to evaluate the complications of laparoscopic cholecystectomy in our centre.
Methods: 1628 LCE operations were analyzed, which performed in period 2010-2018. Among them 1016 patients (62,4%) had GS with acute cholecystitis, 612 (37,6%) – chronic cholecystitis. Woman – 75,8% (n = 1234), man – 24,2% (n = 394), average age was 49,5±6,6 year.
Results: Intraoperative and early postoperative complications

(with conversion) was in 69 (4,2%) patients. The conversion to laparotomy was in 49 (3,0%) cases. Cause of conversions was: adhesive infiltrative process of hepatoduodenal ligament – 36 cases (73,6%), common bile duct injury – 6 (12,2%), liver abscess detection – 1 (2,0%), atypical cystic artery – 1 (2,0%), massive bleeding from cystic artery – 2 (4,1%), bleeding from gallbladder bed – 2 (4,1%), duodenum wall injure – 1 (2,0%). In early postoperative period observed following 15 (0,9%) complications: bile leakage – in 9 patients (in 5 patients it stopped on their own), bleeding – 2, sub-hepatic infiltrate – 4, choleperitonitis after injury of extrahepatic bile duct – 3. Three patients had relaparoscopy due to bile leakage from cystic duct stump (1 case) and bleeding from the cystic artery (2 cases). Reasons for early 4 laparotomies were postoperative bleeding – 1 patient, bile leakage – 3 cases. In three cases with bile leakage, we held suturing the bile duct wall. Abdominal wall wound inflammatory complications were 5%. One patient after LCE had pulmonary artery thromboembolism and died.

Conclusions: Our study of intraoperative and early postoperative complications of LCE can eliminate risk factors that contribute to development. Careful comprehensive preoperative examination to the prediction of the complexity of surgical intervention will improve results of LCE.

Keywords: Cholecistectomy, Laparoscopic, Complication, Gallbladder stone

PE-287

The Value of Lymphadenectomy in Surgical Resection of Perihilar Cholangiocarcinoma

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Aims: Surgical resection is the only potentially curative treatment for patients with resectable perihilar cholangiocarcinoma (PHC). There is still no consensus on the value of lymphadenectomy despite evidence indicating lymph node (LN) status is an important prognostic indicator for postoperative long-term survival. We sought to perform a meta-analysis to summarize the current evidence on the value of lymphadenectomy among patients undergoing surgery for PHC.

Methods: The PubMed, Embase, Medline and Cochrane Library were systematically searched for studies published before July 2018 that reported on lymphadenectomy at the time of surgery for PHC after curative surgery.

Results: 7,748 patients from 28 studies were included in the meta-analysis. No survival benefit was identified with increased number of LN resected (all P > 0.05). Meanwhile, overall LN status was an important prognostic factor. Patients with lymph node metastasis had a pooled estimate hazard ratio of death that was over two-fold higher than patients without lymph node metastasis (HR 2.07, 95% CI 1.65–2.59, $P < 0.001$). The examination of 5 LNs on histology was associated with better staging of lymph node status and stratification of patients into positive or negative LN groups.

Conclusions: While the extent of LN dissection was not associated with a survival benefit, examination of more than 5 LNs better staged patients into positive or negative LN groups with a lower risk of nodal understaging.

PE-288

Who Can Benefit from Adjuvant Transcatheter Arterial Chemoembolization after Surgical Resection of Hepatocellular Carcinoma?

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Aims: Although adjuvant transcatheter arterial chemoembolization (TACE) has been used to prevent postoperative recurrence after hepatocellular carcinoma (HCC) resection, the survival benefits of adjuvant TACE remain controversial. To evaluate the effectiveness of adjuvant TACE for HCC, as well as identify patient populations that might benefit from adjuvant TACE.

Methods: The PubMed, Embase, Medline and Cochrane library were systematically searched for studies published before October 2018 that compared adjuvant TACE versus surgery alone for HCC. The primary endpoints were overall survival (OS) and disease-free survival (DFS). Patients with large HCC (≥ 5 cm), multinodular HCC, microvascular invasion (MVI), or portal vein tumor thrombosis (PVTT) were analyzed in subset analyses.

Results: Twenty-five studies with 6,977 patients were included in the analytic cohort. The pooled analysis demonstrated that adjuvant TACE was associated with a better OS and DFS [HR: 0.67 and 0.67, both $P < 0.01$]. In subgroup analyses, pooled results revealed that adjuvant TACE was associated with an improved OS and DFS in patients with multinodular HCC (HR: 0.79 and 0.31, both $P < 0.01$), MVI (HR: 0.62 and 0.67, both $P < 0.01$), or PVTT (HR: 0.49 and 0.58, both $P < 0.01$), but not among patients with large HCC (≥ 5 cm) (HR: 0.82 and 0.97, both P > 0.20).

Conclusions: Postoperative adjuvant TACE may be effective to improve OS and RFS in selected patients with multinodular HCC, or HCC with MVI or PVTT. Future randomized controlled trials are needed to better define the benefit of adjuvant TACE.

PE-289

Exosomal miRNA-106b from Cancer-Associated Fibroblast Promotes Gemcitabine Resistance in Pancreatic Cancer

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Aims: Gemcitabine (Gem)-based chemotherapy is commonly used to treat pancreatic ductal adenocarcinoma (PDAC). However, intrinsic and acquired resistance to Gem therapies remains a challenge for PDAC patients. Cancer-associated fibroblasts (CAFs), comprising the majority of the tumor bulk, play vital roles in regulating tumor progression and drug resistance by transferring exosomes (Exo) to cancer cells.
Methods: We investigated the potential role of CAFs in the resistance of pancreatic cancer cells to Gem and revealed its underlying mechanism.
Results: We found that CAFs were innately resistant to Gem. The conditioned medium (CM) and exosomes derived from CAFs contributed to Gem resistance of pancreatic cancer cells, and Gem treatment further enhanced the effect of CAFs or CAFs-Exo on pancreatic cancer cells survival. We identified that miR-106b level was upregulated in CAFs and CAFs-Exo following Gem treatment. And miR-106b was directly transferred from CAFs to the pancreatic cancer cells by the mediation of exosomes. Furthermore, pretreatment of CAFs with miR-106b inhibitor suppressed miR-106b expression in CAFs-Exo, and resulted in a decreased resistance of pancreatic cancer cells to Gem. Finally we identified that miR-106b promoted Gem resistance of cancer cells by directly targeting TP53INP1.
Conclusions: CAFs-mediated Gem resistance in PDAC is partially related to overexpression of miR-106b in CAFs-Exo and that inhibiting the transfer of CAFs-derived miR-106b might be a potential treatment to alleviate Gem resistance.

PE-290

The Regulation Mechanism of HEATR1 on the Chemosensitivity of Gemcitabine in Pancreatic Cancer

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Aims: Our team discovered a chemosensitivity related gene of gemcitabine called HEATR1(HEAT repeat containing 1) and published the research on Cancer Research in 2016. Here our team aim to discover the novel functional genes correlated with HEATR1 in sensitizing pancreatic cancer cells to gemcitabine.
Methods: We first knocked down HEATR1 expression in pancreatic cancer cell line PANC-1 (HEATR1-KD) with gemcitabine treatment. Total RNAs were subjected to gene chip analysis to find out differential expression genes (DEGs) (Fold change >1.5 and *P* value < 0.05) between two groups (HEATR1 KD vs NC). DEGs were further analyzed and 30 genes were selected. Selection principles were 1) Literature review was carried out to ensure selected DEGs were not reported with functions previously in pancreatic cancer; 2) Trans-membrane protein encoding genes were ruled out as their low knock-down efficiency; 3) Fold change of selected DEGs were larger than 2. These 30 selected genes were tested their expression levels in HEATR1-KD PANC-1 cells using quantitative PCR. Among the top 20 genes with high expression levels were subjected to high content screening (HCS) in HEATR1-KD cells to testify whether they could affect cell proliferation activity when knock down their expressions, with or without gemcitabine treatment respectively.
Results: Our study proposed that silencing ZNF185 could coordinate with gemcitabine to attenuate cell proliferation ability, while silencing ZNF185 alone did not affect cell viability. Meanwhile, ZNF185 fold change was 4.52 in gene chip analysis.
Conclusions: ZNF185 may play a significant role in pancreatic cancer cells responding to HEATR1 mediated chemotherapeutic sensitivity.

PE-291

Metformin Inhibited Pancreatic Cancer Growth by Upregulating miR-143/145 Cluster and Suppressing MAPK Signaling Pathway

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Aims: Accumulating evidence suggests that metformin treatment is associated with decreased risk and better survival outcome of pancreatic cancer (PC) in patients with diabetes. Besides, our previous study revealed that miR-143 was as essential regulator of cancer glycolysis and miR-143/145 cluster was reported as a tumor suppressor in a range of cancer. The aim of present study was to investigate whether miR-143/145 cluster was associated with antitumor effect of metformin in PC and its potential mechanism.
Methods: We analyzed miRNA sequencing dataset of PC from NCBI (GSE37406) to identify miRNA that were differently expressed between metformin treatment and control group. MiR-143/145 expression level were determined by qRT-PCR, and expression level of target protein were detected by western blot. Potential target genes of miR-143/145 were identified by bioinformatic analyses and confirmed by luciferase reporter assays. Furthermore, biological consequences of miR-143/145 alternation and metformin treatment were examined by cell

proliferation, invasion, and apoptosis assays *in vitro* and by patient derived xenograft models *in vivo*.

Results: MiR-143/145 was upregulated in metformin-treated PC. Overexpression of miR-143/145 inhibited proliferation and induce apoptosis of PC *in vitro*. Metformin inhibited tumor growth while downregulation of mir-143/145 cluster downstream of metformin treatment abrogated its antitumor effect both *in vitro* and vivo. Furthermore, miR-143/145 cluster directly targeted 3′-UTR of MAPK and AKT and repressed their expression. Low MAPK and AKT expression level correlated with better prognosis in PC.

Conclusions: Our data demonstrated the pivotal role of metformin/miR-143/145 cluster/MAPK axis and suggested miR-143/145 cluster as a candidate therapeutic target in PC.

PE-292

Acute Pancreatitis Induced by Etoposide-Lobaplatin Combination Chemotherapy Used for the Treatment of Lung Cancer

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Aims: Drug-induced pancreatitis (DIP) is a rare type of pancreatitis that is not usually observed in the clinical practice. It is generally difficult to distinguish form acute pancreatitis (AP) induced by other causes.

Methods: Here, we report a 62-year-old Chinese female patient with "small cell lung cancer" as the initial presentation. Because the patient could not bear the surgical treatment, the chemotherapy composed of lobaplatin and etoposide was performed. Three days later, the patient displayed sudden abdominal pain, distension, nausea, and vomiting without obvious inducements. Laboratory tests showed that the levels of serum and urine amylase were enhanced; abdominal computed tomography (CT) result showed the enlargement of the pancreas, peripancreatic effusion, and a rough edge, which suggested the diagnosis of AP. The patient had no history of biliary tract disease, alcoholism, binge overeating, hyperlipidemia, and hereditary pancreatitis. The patient was diagnosed with DIP and the chemotherapy was stopped at once. Then we performed fluid resuscitation, pain alleviation, prophylactic antibiotics, and nutritional support, etc on the patient. Later, the patient's clinical symptoms were obviously relieved, and she recovered successfully.

Results: The chemotherapy was continued, but later, the patient showed abdominal pain, distension, nausea, and vomiting again. The levels of serum amylase and urine amylase were enhanced again. Further imaging examination strongly indicated the recurrence of AP.

Conclusions: We should raise awareness of the clinicians regarding DIP, thereby enabling its timely diagnosis and accurate treatment, as well as promoting the rational and safe use of drugs.

PE-293

Exosomes and Pancreatic Diseases: Status, Challenges, and Hopes

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Aims: Pancreatic disease is a complicated and dangerous clinical condition involving the disruption of exocrine or endocrine function, including pathologies such as acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC). PC has one of the highest mortality rates, due to insufficient diagnosis in early stages.

Methods: There remains a lack of efficient treatment options for disease etiology in AP or CP. Thus, the identification of new therapeutic targets and reliable biomarkers is required. As essential couriers in intercellular communication, exosomes have recently been confirmed to play an important role in pancreatic disease, but the specific mechanisms at play are still unknown.

Results: In this review, we discuss current research progress on exosomes, particularly with respect to their role as intracellular couriers, biomarkers, and therapeutic vectors for pancreatic diseases.

Conclusions: We summarize the current knowledge of exosomes in pancreatic disease, with respect to diagnosis, molecule mechanism, and treatment, proposing new ideas for the study of pancreatic disease.

PE-294

Immunogenicity of Neoplastic Cells in PDA (Review)

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Aims: Immune-based therapies that enhance the ability of cytotoxic T cell to target tumor cells showed a moderate promise to several solid tumors. However, the neoplastic cells in pancreatic cancers are refractory to all immune-based therapies or the combination of immune-based therapies with chemotherapies including PD-L, IDO target therapies. Multiple mechanisms cause the insensitivity of neoplastic cells to immune-based therapies including low immunogenicity of pancreatic cancer neoplastic cells.

Methods: The recent study in Japan has revealed the tumor-infiltrating CD4+ and CD8+ T-cells as independent prognosticators useful for evaluating the immune microenvironment of PDC. Using immunohistochemistry, the examination and analysis of tumor-infiltrating cells pan-macrophages, M1, CD163+ or CD204+ M2 macrophages (M2), CD66b+ neutrophils, CD4+

T cells, CD8+T cells, regulatory T cells in 212 cases of PDC, it is anticipated that tumor-infiltrating immune/inflammatory cells would be useful hallmarks for evaluating and monitoring the characteristics of a tumor immune microenvironment.
Results: Several studies showed that immunocheck point agents showed a promising therapeutic effect to inhibit murine pancreatic cancer development by enhancing the immonogenicity of pancreatic tumor cells. Recongnizing the neoplastic cells by cytotoxic T cells is the first step in exerting cytotoxic effects of tumor killing T cells.
Conclusions: Collectively, the precise strategy of PDA treatment remained unclear but based on recent studies and trials, the most promising target to suppress cancer cells is immunotherapy. The dual mechanism of both increasing CD4+ and CD8+ T-cells along with deactivating the tumor microenvironment, as well as drug combination therapy might significantly improve the response to chemotherapy and overall survival.

PE-295

Pancreatic Stellate Cells Promote Epithelial-Mesenchymal Transition of Cancer Cells by Notch-3 Promoter Demethylation

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Aims: Pancreatic stellate cell(PSC) promoted epithelial-mesenchymal transition(EMT). However, the potential mechanism had not been fully elucidated. The aim of this study was to explore the effect of Notch-3 on EMT of PANC-1 cells induced by PSC.
Methods: We explore the effect of PSC on PANC-1 cell EMT. The potential signal pathway involved in EMT is determined by adding different inhibitors. The role of Notch-3 in EMT process is verified through Notch-3 siRNA transfection. Bisulphite sequencing PCR and chromatin immunoprecipitation are performed to explore the methylation status of Notch-3 promoter. To confirm the relationship between EMT, Notch-3 status and patient survival, Kaplan-Meier analysis is performed.
Results: After co-culture with PSC, the ability of migration is significantly enhanced, and the PSC can also induce EMT phenomenon of PANC-1. Meanwhile, the Notch-3 expression is also promoted. The effect blocked by Notch signal pathway inhibitor(L1790) and Notch-3 siRNA revealed the critical role of Notch-3 in EMT process. The methylation status of three CpG islands located in promoter region of Notch-3 has been uninfluenced after co-culture with PSC. However, immunoprecipitation reveals a significant increase in hmC for Notch-3 promoter. Our study also demonstrate that Notch-3 level is positively correlated with Vimentin and negatively with E-cadherin expression in pancreatic cancer patients. Overexpression of Notch-3 also predicts the poor prognosis of pancreatic cancer.
Conclusions: PSC induces Notch-3 expression by demethylation and promote EMT phenotype of PANC-1 cell. EMT and Notch-3 are the poor prognostic factors in pancreatic cancer patients. Notch-3 might be a potential target for treatment of pancreatic cancer.

PE-296

Smad4 Inhibits Cell Migration via Suppression of KPNA4 and MMP26 in Human Pancreatic Cancer Cells

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Aims: Smad4 was known as a tumour-suppressor gene that frequently mutates in pancreatic cancer. Previous studies indicated that Smad4 is the central component of the bone morphogenetic protein (BMP) signaling pathway, forming a complex with p-smad1/5/9 and regulating the target genes in the nucleus. It is attractive to explore the potential genes regulated by the complex and uncover the molecular mechanism of Smad4 in pancreatic cancer cells.
Methods: The enrichment of BMP signaling pathways in three GEO databases was analyzed by GSEA software. Immunohistochemistry was used to detect the expression of Smad4 in pancreatic cancer and adjacent tissues. ChIP-sequence analysis explored the target genes regulated by Smad4/p-smad1/5/9 complex. The cell migration and invasion ability were assessed by Transwell assays. The nude mouse lung metastasis model was used to detect the invasive ability of pancreatic cancer cell lines *in vivo*.
Results: The BMP signaling pathway is hyperactivated in pancreatic cancer, and its key molecule Smad4 is highly expressed in 80 pancreatic tissue specimen and is related with prognosis. Ectopic expressed Smad4 in Smad4-deficient BxPC-3 significantly inhibited cell migration and invasion. Downregulated Smad4 in Mia-Pa-Ca-2 dramatically promoted cell migration and invasion, and we demonstrated that p-Smad1/5/9-Smad4 complex can regulate the expression of KPNA4 and MMP26, and hence regulate the migration and invasion ability of pancreatic cancer cells.
Conclusions: The present findings indicate that Smad4 may suppress the expresion of KPNA4 and MMP26 mediated by p-smad1/5/9 and inhibit the tumor characteristics of pancreatic cancer cells.

PE-297

General Surgery

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Aims: Laparoscopic, Pancreaticoduodenectomy,Pancreatic Fistula, Pancreatic-enteral Reconstruction
Methods: The most difficult part in LPD is pancreatic-enteral reconstruction.We present our new method: Single stitch pancreatic duct suture with drainage tube for pancreaticojejunostomy (SSPDSPJ) in LPD. During April 2016 to September 2017,

patients who underwent LPD with SSPDSPJ at our hospital were included. Patients and their families were informed of this procedure before operation. Clinical data including estimated blood loss, operative time, pancreaticojejunostomy (PJ) time and postoperative data such as hemorrhage, pancreatic fistula, bile leakage, delayed gastric empty were collected prospectively. The definition and grade of complications were recorded according to the ISGPS definition.

Results: Eighty patients were included and no patients was converted to open surgery. The median operation time was 260 minutes (range from 200 minutes to 560 minutes). The median pancreatic-jejunum reconstruction time was 26 minutes (range from 18 minutes to 40 minutes). The median estimated blood loss was 160 ml (range from 30 to 800 ml). 10 patients (12.5%) underwent blood transfusion during operation. Thirty-one patients had firm pancreas and 49 patients had soft pancreas. The median diameter of pancreatic duct was 3 mm (range from 1 to 8 mm). Eight patients (10.0%) suffered from grade B pancreatic fistula, no patient with grade C fistula. Four patients (5%) suffered from bile leakage and 5 patients (6.3%) suffered from delayed gastric empty. Three patients (3.8%) had postoperative hemorrhage. No 30-day mortality occurred.

Conclusions: SSPDSPJ is a safe technique. Besides, it is simple, efficient, reproducible and easy to grasp that can shorten the learning curve time.

PE-298

Lipopolysaccharide Increase PD-L1 Expression in Pancreatic Tumor via TLR4/MyD88/NF-κB Pathway

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Aims: The programmed death ligand 1(PD-L1) is essential for tumor cells to keep immune escape and related to poor prognosis. Previous studies have identified that bacteria lipopolysaccharide (LPS) can affect the expression of PD-L1 on immune cell, but its effect on the tumor cell hasn't been investigated. This study is aimed at whether lipopolysaccharide (LPS) can induce PD-L1 on pancreatic tumor.

Methods: The effect of LPS on the two pancreatic tumor cell lines (Panc1 and Bxpc-3) was analyzed *in vitro*. The level of PD-L1 and its relevant pathway were verified by real time PCR and western blot.

Results: The expression of PD-L1, Toll-like receptor 4(TLR4) and MyD88 was upgraded after LPS stimulation in a concentration-dependent way and the nuclear factor-κB (NF-κB) pathway is also activated. TLR4-sh plasmid and MyD88-sh plasmid was transfected into cell lines respectively. Correspondingly, PD-L1 expression was obviously downgraded comparing with their control groups. Meanwhile, the effect of LPS was neutralized when cells were pre-treated with NF-κB pathway specific inhibitor PDTC and Bay-11-7082. Furthermore, we observed that p65 could bind to the PD-L1 promoter by Chip assay.

Conclusions: Overall, our study has shown that LPS can induce PD-L1 expression in pancreatic tumor via TLR4/MyD88/NF-κB pathway. Intervening LPS *in vivo* might be another way to reduce PD-L1-mediated immune escape.

PE-299

Circulating Tumor Cells with Epithelial-Mesenchymal Transition Features Predict Metastatic Outcome in Pancreatic Cancer

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Aims: To clarify the metastatic potential of CTCs with mesenchymal phenotypic (mCTCs) characteristic in pancreatic cancer (PC).

Methods: Among both localized (n = 21) and metastatic (n = 14) patient populations, blood samples (7.5 ml each) were drawn from peripheral vein. Of them, portal and peripheral blood samples were simultaneously collected intra-operatively in 19 patients following surgical dissection prior to tumor removal. All samples were analyzed for CTCs with immunomagetic negative enrichment together with 4-channel immunofluorescence against Cytokeratin, Vimentin, DAPI and CD45.

Results: CTCs were detected in 91.4% (32/35) and 100.0% (14/14) of patients with AJCC stage Ⅰ-Ⅲ and stage Ⅳ tumors, respectively. 21 localized patients had a mean count of (148.9±159.9) CTCs/7.5 mL in peripheral blood, compared with a mean count of (279.5±297.5) CTCs/7.5 mL in 14 metastatic patients (P = 0.127). Meanwhile, the mCTCs percentage tended to be higher in metastatic group, implying that mCTCs may be a risk factor for metastatic disease. Among 19 patients received operations, there was a mean count of (148.1±152.8) CTCs/7.5 mL in peripheral blood vs. (252.0.4±220.9) CTCs/7.5 mL in portal vein (P = 0.170). However, the mCTCs percentage of portal vein was significantly different from that of peripheral vein (P = 0.048), meaning a obvious spatial heterogeneity in epithelial and mesenchymal composition during circulation. The clinical significance of distant composition warrants further exploration.

Conclusions: CTCs with mesenchymal phenotype may in part represent tumor clones with high metastatic potential, suggesting that this special subtype CTC-positivity identifies patients with occult systemic disease and neoadjuvant therapy may improve the prognosis.

PE-300

Serum Lipid Levels and the Risk of Gallbladder Stones: A Population-Based Study in China

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Aims: Gallstones are the cause of a majority of biliary tract discomfort. Although many community-based studies have addressed the risk factors for gallstone disease (GSD), little is known about GSD prevalence and risk factors in Chinese populations.
Methods: From January 2014 to January 2015, participants (N = 216,161) were recruited by Meinian Onehealth Healthcare (Group) Co., Ltd. They received a physical examination, and GSD was determined by ultrasound.
Results: The prevalence of GSD was 8.1%. Risks of GSD were similar between males and females in all age groups. Risk factors for gallstones include body mass index, waist circumference, waist-to-hip ratio, and physical activity, as well as biological factors such as age, sex, and elevated blood lipid levels. Serum lipid levels of GSD were statistically different from controls in total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (H-DL), low-density lipoprotein cholesterol (LDL), and apolipoprotein B (APOB). Furthermore, TC > 5.00 mmol/L, TG > 1.39 mmol/L, HDL < 1.19 mmol/L, LDL > 3.04 mmol/L, and APOB > 0.97 mmol/L were risk factors for gallstones.
Conclusions: Serum lipid levels are associated with GSD. TC, TG, LDL, and APOB are risk factors, while HDL is a protective factor.

PE-301

Any Time Laproscopic Cholecystectomy in Moderate to Severte Acute Cholecystitis without Septic Shock: A Prospective Cohort Study

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Aims: In laproscopic cholecystectomy in Acute cholecystitis most authors recommond surgery within first 72 hours. We offer laproscopic cholecystectomies in every patient of acute cholecystitis regardless of timing of presentation.
Methods: We prospectively analyzed outcomes of our protocol of any time acute cholecytitis. We perform laproscopic cholecystectomies within first 24 hour of presentation regardless of starting of symptomps.All the data were prospectivly analyzed.
Results: We performed 110 laproscopic cholecystectomies between april 2016 to january 2019. We prefer single dose pre operative antibiotic in all laproscopic cholecystectomies. Total 79 patients were having acute cholecystitis. 67 patient were having grade 2 and 12 patients were having grade 3 cholecystitis according to tokyo guidelines. 50 patients were presented after more than 72 hours after attack. 21 patient presented more than 48 hours but less than 72 hours. 8 patients presented within 24 hours. Mean duration of presentation was 120 hours. 5 patients presented after more than 7 days. 2 patients were converted to open,in 3 patient underwent lap subtotal cholecystectomy due to difficult calot triangle. Out of these only 2 patient developed port site infection and 3 patients developed bilioma.
Conclusions: Any time laproscopic cholecystectomy should be the rule in experienced centre.

PE-302

Post Operative Antibiotics Are Unnecessary Even in Moderate to Severe Cholecystitis According to Tokyo Guidelines: A Prospective Cohort Study

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Aims: Single dose antibiotic is recommended for laproscopic cholecystectomy, for symptomatic gall stones. However very few studies are there for subgroup grade-2 and grade-3 cholecystitis according tokyo guidelines 2018.
Methods: We prospectively analyzed out comes of our protocol of no post operative antibiotics in grade-2 and grade 3 (moderate to severe) acute cholecytitis according to tokyo guidelines. We perform laproscopic cholecystectomies within first 24 hour of presentation to us without considering time since attack if patient is not in septic shock where we follow survival sepsis guidelines and also perform percutaneous cholecystostomy.
Results: We peroformed 101 laproscopic cholecystectomies between april 2016 to january 2019.We prefer single dose pre operative antibiotic (third generation chephalosporin) in all laproscopic cholecystectomies and no post operative antibiotics. Total 74 patients were having grade 2 or grade 3 cholecystitis. 64 patient were having grade 2 and 9 patients were having grade 3 cholecystitis. One patient was having grade 3 cholecystitis and was having septic shock so he was managed with per cutaneous cholecystostomy and according to survival sepsis prtocol and lap choly was done after 72 hours and hence excuded from study. Out of 73 patient included in study 2 patient were converted to open,in two patient we performed lap subtotal cholecystectomy due to difficult calot triangle. Out of these only 1 patient developed port site infection and two patient developed bilioma which was managed by percutaneous drainage.
Conclusions: Post operative antibiotics are unnecessary in grade-2, grade-3 acute cholecystitis without septic shock.

PE-303

Preprocurement Pancreas Allocation Suitability Score Does Not Correlate with Long-Term Pancreas Graft Survival

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Aims: Within recent years, more marginal donors have been offered to Eurotransplant. To help identify suitable pancreas-donors, the Eurotransplant Pancreas Advisory Committee introduced a donor score system (P-PASS). Little is known about the influence of P-PASS on long-term pancreas graft survival.
Methods: From June 2004 to September 2018, we performed 405 pancreas transplantations. In a retrospective study we analyzed P-PASS in 318 cases. Pancreas grafts from donors with P-PASS < 17 (n = 146) analyzed for graft and patient survival as well as for surgical complications were compared with donors of a PASS > or = 17 (n = 172). The mean follow-up was 7.2 +/- 4.3 years.
Results: Recipient characteristics were comparable in both groups. Mean P-PASS was 16.7 +/- 2.7 for both groups: 14.3 +/- 1.5 for P-PASS < 17 and 18.8 +/- 1.6 for P-PASS > or = 17. Pancreas graft survival rates for 1, 5, and 10 years were 85%, 77%, and 73% among P-PASS < 17 and 81%, 73%, and 64% among P-PASS > or = 17 groups (P = .12). The relaparotomy rate was significant higher (38.7% vs 28.7%) and duration of hospital treatment longer (40.2 vs 32 days) in the P-PASS > or = 17 group (P < .05).
Conclusions: The data demonstrated that utilization of pancreas grafts from donors with a P-PASS > or = 17 resulted in good overall outcomes and could expand the organ donor pool. Complications requiring relaparotomy were more frequent among patients after transplantation from donors with higher P-PASS.

PE-304

Microvessel Density and Impact of Angiogenesis on Survival of Resected Pancreatic Cancer Patients: A Systematic Review and Meta-Analysis

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Aims: Angiogenesis plays a major role in tumor progression and metastasis; however, its role in pancreatic cancer (PC) remains unclear. The aim of the study was to explore the cumulative evidence concerning the impact of microvessel density (MVD), an estimator of angiogenesis, on resected PC patients.
Methods: A systematic review of literature and a meta-analysis of relevant reports were performed. Overall survival and disease-free survival were scrutinized.
Results: One thousand five hundred patients were analyzed. Overall survival (hazard ratio, 2.0; 95% confidence interval, 1.57-2.54; P < 0.001) and disease-free survival (hazard ratio, 1.99; 95% confidence interval, 1.24-3.2; P = 0.004) were in favor of the low-MVD group. Use of CD105 antibody and of a computerized image analysis system was found to significantly reduce the heterogeneity. Disease staging, tumor location, and grading showed significant effect on survival.
Conclusions: High-MVD expression was strongly associated with poorer survival and recurrence among resected PC patients, demonstrating a negative prognostic value. Use of CD105 antibody and of a computerized image analysis system is recommended in future studies because they reduce heterogeneity of results. The potential role of MVD as a marker to select PC patients who would benefit from antiangiogenetic treatment should be further explored in clinical trials.

PE-305

Potential Value of Serum Total IgE for Differentiation between Autoimmune Pancreatitis and Pancreatic Cancer

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Aims: Autoimmune pancreatitis (AIP) is associated with a marked elevation of serum total IgG_4. Although there is evidence of autoimmunity in AIP, there are also signs of an allergic nature of its pathogenesis.
Methods: Therefore, we determined both IgE and IgG_4 in 13 patients with AIP, in 12 patients with pancreatic carcinoma and in 14 patients with atopic allergy and investigated the relationship between IgE and IgG_4. Total IgG_4 was determined by automated nephelometry and total IgE by automated enzyme fluoroimmunoassay. Both total IgE and total IgG_4 levels in patients with AIP were significantly higher than those in patients with pancreatic carcinoma (P = 0.0004 and P = 0.015, respectively). There was a significant correlation between the total IgE and total IgG_4 levels in patients with AIP and patients with atopic allergy (r(s) =0.82, P = 0.0006 and r(s) =0.88, P < 0.0001, respectively).
Results: The IgE/ IgG_4 ratio in sera from patients with atopic allergy was significantly different (P = 0.0012) from this ratio in sera from patients with AIP.
Conclusions: These results suggest that analysis of total IgE in serum might be useful in the differentiation between autoimmune pancreatitis and pancreatic carcinoma.

PE-306

Conservative and Surgical Management of Pancreatic Trauma in Adult Patients

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Aims: The management of pancreatic trauma is complex. The aim of this study was to report our experience in the management of pancreatic trauma.
Methods: All patients hospitalized between 2010 and 2018 for pancreatic trauma were included. Traumatic injuries of the pan-

creaswere classified according to the American Association for Surgery of Trauma (AAST) in five grades. Mortality and morbidity were analyzed.
Results: A total of 30 patients were analyzed (mean age: 38±17 years). Nineteen (63%) patients had a blunt trauma and 12 (40%) had pancreatic injury ≥ grade 3. Fifteen patients underwent exploratory laparotomy and the other 15 patients had nonoperative management (NOM). Four (13%) patients had a partial pancreatectomy [distal pancreatectomy (n = 3) and pancreaticoduodenectomy (n = 1)]. Overall, in hospital mortality was 20% (n = 6). Postoperative mortality was 27% (n = 4/15). Mortality of NOM group was 13% (n = 2/15) in both cases death was due to severe head injury. Among the patients who underwent NOM, three patients had injury ≥ grade 3, one patient had a stent placement in the pancreatic duct and two patients underwent endoscopic drainage of a pancreatic pseudocyst.
Conclusions: Operative management of pancreatic trauma leads to a higher mortality. This must not be necessarily related to thepancreas injury alone but also to the associated injuries including liver, spleen and vascular trauma which may cause impaired outcome more than pancreas injury.

PE-307

Hepaticojejunostomy (HJ): How We Do It?

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Aims: Hepaticojejunostomy (HJ) is one of the common surgical procedures in hepatobiliary and pancreatic (HBP) surgery to treat both benign and malignant diseases. There were few studies in which an attempt has been made to describe the detailed procedure of HJ.
Methods: The total of 128 operations were performed. Most of the patients had recurrent pyogenic cholangitis (RPC) and had undergone Roux-en-Y HJ with permanent access. Anastomosis was done with both extrahepatic and intrahepatic bile duct. Construction of HJ was performed by detailed step-by-step method. PDS or Vicryl suture was used. The size of suture depends on the opening of the anastomosis. The anastomosis was made using interrupted stitches for the anterior layer and continuous fashion posteriorly. For special consideration, mucosal stitches and vertical incision to CHD were performed for smaller anastomosis, and in multiple bile duct openings, neighboring bile ducts were transformed into a common channel by inserting stitches between them.
Results: There were three mortalities in the study. All cases were associated with major bile leak. Two patients had RPC with cholangitic abscess. The other patient had periampullary CA who had undergone Whipple's operation. Six patients had minor bile leak that recovered with conservative treatment.
Conclusions: In this paper, the proposed method for HJ is a reliable and feasible technique. It can be applied in a variety of diseases. The method is not a recommendation or procedural modification but a useful surgical option which follow the standard principles of anastomosis.

Liver Transplantation

PE-308

Program of Transplant Organization to Coordinate the Development of Organ Donation in Kazakhstan

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Aims: The aim of this study to evaluate the progress of organ transplantation procedure.
Methods: In recent years organ transplantation has become a well-established procedure for management of renal, liver, cardiac, and respiratory failure. In spite of that, a shortage of organs still remains a serious problem for the full development of these therapeutic approaches in Kazakhstan. The first kidney transplantation was performed in Kazakhstan in 1979, approximately 40 years ago. The operation itself was technically successful, but the lack of immunosuppression caused graft rejection, and the patient died after a few days.
Results: Due to government policy, an organized organ transplant program started more than 4 years ago and the program was supported by the Ministry of Health. During this period a well-designed program of transplant organization has been established. In Kazakhstan, each potential donor hospital has a transplant coordinator who is responsible for the whole process of organ procurement. Eleven transplant centers work currently in Kazakhstan, and 557 transplantations have been performed up to the middle of the year 2015. We found that renal, liver and cardiac transplants increased since coordination program started.
Conclusions: We conclude that this program was successful in Kazakhstan and organ donation, procurement, and transplantation would become commonplace events to solve the problem of the organ donor shortage.
Keywords: Transplantation, Liver, Coordination, Development

PE-309

Frequency and Main Risk Factors of Ventral Site Hernia Development in Patients Liver Transplantation

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Aims: The main purpose of this study was to perform a retrospective analysis for risk factors of ventral site hernia (VSH) in a

group of patients after living-donor liver transplantation with abdominal midline incisions.

Methods: Data collection involved the review of age, body mass index (BMI), smoking, and the presence of additional medical disorders, operative complications, postoperative care, surgical infections (SI), chemotherapy, and duration of follow-up. Appropriate statistical tests were used.

Results: Thirty-five patients were operated with midline incisions. 5 patients had VSH with a rate of 25% incidence. In our study, the main risk factors as age, BMI, operative complications, SI, chemotherapy, and duration of follow-up were statistically significant.

Conclusions: The presence of independent risk factors should be taken over by an oncologist in order to prevent the formation of VSH in a long-term follow-up. In the following studies it remains to provide evidence that, in the presence of several risk factors, the use of individual treatments (using meshes, etc.) is necessary.

Keywords: Liver, Transplantation, Hernia, Ventral, Operation

PE-310

Portal Vein Thrombosis in Patients with End-Stage Liver Disease on the Waiting List

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Aims: Among the patients with end-stage liver diseases on the waiting list, the portal vein thrombosis (PVT) complicates the liver transplant operation and theoretically disturbs survival. The aim of this research is to find the consequence of PVT on the survival benefit of liver transplantation

Methods: From January 2015 to February 2018 patients with end-stage liver diseases were treated electively by liver transplantation performance Aqtobe Medical Center. Data collection involved the review of age, body mass index (BMI), smoking, and the presence of additional medical disorders, operative complications, postoperative care, surgical infections (SI) and duration of follow-up. Appropriate statistical tests were used. Also by sequential stratification, we estimated the liver transplant survival benefit by MELD score and PVT status

Results: The occurrence of described PVT among liver transplant recipients was not a predictor of waiting list mortality but was a forecaster of posttransplant mortality. With all of this, transplant advantage was not significantly different for patients with PVT vs. without PVT

Conclusions: PVT does not disturb waiting list mortality, but it is related to meaningfully advanced posttransplant mortality. Transplant surgeons should sensibly reflect the risks of liver transplantation in clinically stable patients who have PVT

Keywords: Waiting list, Liver, Portal vein, Thrombosis, End-stage, Transplantation

PE-311

Influence of Adult Living Donor Liver Transplantation on the Waiting List in Kazakhstan

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Aims: Living donor liver transplantation (LDLT) has become improved access to a lifesaving transplant for patients with end-stage liver disease especially in zones where waiting time mortality is high and availability of deceased donor organs is shortened. Due to the collaborative program with Seoul National University Hospital and several hospitals in Kazakhstan, this treatment option becomes available for our citizens

Methods: This collaboration shows that there are noteworthy risks to the donor, including the risk of death and considerable morbidity, that must be occupied into interpretation before transplant programs board in LDLT. Significant developments in outcomes have been seen over the past years that have now been reported in several centers of our country

Results: In spite of this, living donor liver transplant remains standing. It is well known that centers with more experience have improved outcomes. Upcoming investigation requirements to address best donor assessment, as well as identify the most appropriate LDLT donors and recipients

Conclusions: With all these future studies should help quantify donor risk and recipient outcome, and confidently permit progress and development of the procedure

Keywords: Living donor, Waiting list, Liver, Transplantation

PE-312

Pure Laparoscopic Versus Open Right Hepatectomy in Live Liver Donors: A Propensity Score Matched Analysis

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Aims: Pure laparoscopic donor right hepatectomy (PLDRH) has been reported as a safe and feasible approach. However, its outcomes have not yet been evaluated in a large comparative study. The aim of this study is to describe our experience with PLDRH and to compare its outcomes with those of open right hepatectomy in live liver donors using propensity score matching.

Methods: The medical records of live liver donors between January 2010 and September 2018 at Seoul National University Hospital were retrospectively reviewed. Donors who underwent hepatectomy other than conventional open right hepatectomy or PLDRH were excluded. Propensity score matching study was conducted. Subsequently, 198 donors were included in each group.

Results: The total operation time (270.8 vs. 289.9; $P < 0.001$), time to remove the liver (166.2 vs. 211.4; $P < 0.001$), and

warm ischemic time (3.7 vs. 12.3; $P < 0.001$) were longer in the PLDRH group. The percentage of getting multiple bile duct openings was higher in the PLDRH group (44.9% vs. 56.1%; $P = 0.027$). Δhemoglobin (Hb)%, calculated as ΔHb%= [(preoperative Hb − postoperative Hb)/preoperative Hb] x 100, was lower (21.3% vs 16.6%; $P < 0.001$) and Δaspartate aminotransferase (AST)%, calculated as ΔAST%=[(postoperative AST − preoperative AST)/preoperative AST] x 100 (783.8% vs. 1136.9%; $P < 0.001$), and Δalanine aminotransferase (ALT)%, calculated as ΔALT%=[(postoperative ALT − preoperative ALT)/preoperative ALT] x 100 (912.7% vs. 1358.1; $P < 0.001$), were higher in the PLDRH group. The length of postoperative hospital stay was significantly shorter in the PLDRH group (8.6 days vs. 7.5 days; $P < 0.001$). However, the rate of complications was similar in both groups (10.6% vs. 6.1%; $P = 0.102$).

Conclusions: PLDRH is safe and feasible when performed at an experienced LDLT center.

Keywords: Laparoscopic, Right hepatectomy, Donor hepatectomy

PE-313

Survival among Pediatric Liver Transplant Recipients: Impact of Segmental Grafts

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Aims: Segmental liver transplantation with living donor (LD), reduced cadaveric (Reduced), and split cadaveric (Split) allografts has expanded the availability of size-appropriate organs for pediatric recipients. The relevance of recipient age to the selection of graft type could offer the potential to maximize recipient outcome and donor utilization.

Methods: We conducted a retrospective cohort study among children 12 years of age or less. Cox proportional-hazards analysis was used to explore the association of recipient age and graft type to graft and patient survival. Among children <1 year of age and those 1 to 2 years of age, 3-year LD graft survival was superior to whole cadaveric (CAD) organs, Split grafts, and Reduced grafts (for children <1 year of age: 79.4 vs. 61.5, 66.0, and 61.1%, respectively, $P = .0003$; and for children 1-2 years of age: 79.2 vs 66.9, 57.1, and 63.9%, respectively, $P = .02$). However, in children 3 to 12 years of age, after controlling for multiple donor and recipient factors, LD grafts failed to offer a survival advantage (hazard ratio =.61; 95% confidence interval =.37-1.02) compared to CAD organs.

Results: In an adjusted analysis examining patient survival, there appeared to be minimal association between recipient age and graft type. Much of the difference in graft survival could be attributed to events in the perioperative period.

Conclusions: LD liver transplantation provides improved graft survival in children 2 years of age or less.

Keywords: Liver transplantation, Cadaver, LD graft, Split graft

PE-314

Risk Factor of Delayed Hepaticojejunostomy Site Stricture in Pylorus Preserving Pancreaticoduodenectomy and Its Predicting Nomogram

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Aims: Incidence of anastomotic stricture after hepaticojejunostomy (HJ) in pylorus-preserving pancreaticoduodenectomy is about 4-10% in benign disease, less common in malignancy such as pancreatic ductal adenocarcinoma. It is one of representative long-term complication, still it is not much investigated, such as risk factor for occurrence.

Methods: From Jan 2012 to May 2018, we investigated patients underwent hepaticojejunostomy during pancreaticoduodenectomy by single surgeon in Severance hospital. Patients who occurred HJ stricture confirmed by imaging studies, after 90 postoperative days, during follow-up period.

Results: Total 283 patients were included, and HJ stricture is confirmed in 27 patients (10.5%). Mean Body mass index in HJ stricture patients was slightly lower than NO HJ stricture patients (22.37 vs 23.41, $P = 0.071$) with no statistical significances. However, proportion of postoperative bile leak is significantly higher in HJ stricture group (n = 4, 14.81%) than NO HJ stricture group (n = 9, 3.52%) ($P = 0.026$). In multivariate COX regression, female (HR 0.39, 95% CI 0.16-0.96, $P = 0.039$), bile duct size (HR 1.35, 95% CI 1.08-1.68, $P = 0.007$), postoperative bile leak (HR 3.82, 95% CI 1.25-11.7, $P = 0.019$) were most independent risk factor for HJ stricture. Based on this parameters, 3 year HJ stricture free probability was able to assumed with Harrell's concordance index of 0.7131 (95% CI 0.58-0.82).

Conclusions: Delayed occurrence of HJ stricture after pancreaticoduodenectomy is able to be predicted with powerful risk factors such as female, bile duct size, postoperative bile leak event. With this prediction nomogram, external validation in large cohort and various surgeon is mandatory in near future.

PE-315

A Case of Migration of Cyanoacrylate into Portal Vein after Living Donor Liver Transplantation

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Aims: Gastroesophageal varices bleeding is a major complica-

tion and carries a high mortality in patients with liver cirrhosis. Endoscopic injection of N-butyl-2-cyanoacrylate mixed with lipiodol has been used for hemostasis of bleeding gastric varices. We present a case of migration of injected cyanoacrylate to portal vein after living donor liver transplantation (LDLT).

Methods: A 53-year-old man presented with fever and abdominal pain 3 weeks after LDLT. He had received LDLT due to recurrent bleeding of esophageal and cardiac varices. Tissue adhesive (lipiodol and cyanoacrylate) was injected to cardiac varices 2 months before LDLT. Abdominal CT scan before LDLT showed high attenuation material (lipiodol/cyanoacrylate adhesive) in coronary veins with no evidence of portal vein thrombosis. However, CT scan 3 weeks after LDLT revealed high attenuation material in main portal vein. Fever and thrombocytopenia persisted. Liver enzymes were mildly elevated.

Results: Transsplenic portal vein stent was placed due to protrusion of tissue adhesive into main portal vein after obliteration of gastroesophageal varices. After portal vein stent placement, fever and thrombocytopenia has been improved and portal vein flow was intact.

Conclusions: Treatment of gastroesophageal varices using tissue adhesive is relatively safe. However, migration of injected cyanoacrylate to portal vein should be remembered as a complication caused by tissue adhesive even after LDLT.

Keywords: Living donor liver transplantation, Cyanoacrylate, Portal vein

PE-316

Outcome of Living Donor Liver Transplantation for Secondary Biliary Cirrhosis in Adult: Single Center Experience

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Aims: Although liver transplantation is a definitive cure for secondary biliary cirrhosis (SBC), there is limited data about results of living donor liver transplantation (LDLT) in adults.

Methods: This retrospective study assessed data from 29 SBC patients who had LDLT between December 1994 and July 2018.

Results: The study cohort comprised of 10 males and 19 females, aged 50.0 ± 8.6 years. Except for 3 patients, the rest were diagnosed with secondary biliary cirrhosis from hepatolithiasis, and 25 out of 29 (86.2%) had a history of receiving the hepatobiliary surgery. Model for end-stage liver disease (MELD) score was 18.8 ± 9.4. The major complication rate was 62.1%, and the most common complication was bleeding. The ICU and hospital stay were 24.4 ± 13.8 and 40.9 ± 24.8 days. Four patients died in first month after LDLT; Tow died of rupture of hepatic artery rupture, one died of Intra-cranial hemorrhage, and the other one died of sepsis.

Conclusions: LDLT for patients with SBC is very difficult, and there's a big danger of massive bleeding. Even though operation time is long and there's a lot of bleeding, thorough planning and a meticulous surgical technique that does not cause complications can reduce the mortality rate in LDLT for patients with SBC.

PE-317

Liver Transplantation for Patient with Emergency Indication

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Aims: Decompensate liver cirrhosis is often accompanied by hepatorenal syndrome (HRS) with mortality up to 80%. The aim is improving the results of critical cases of decompensate liver cirrhosis in terminal phase.

Methods: Patient S., 32 years old, female, enrolled with decompensated Primary Liver Cirrhosis, Child-Pugh class C, portal hypertension, esophageal varices II degree, ascites and hydrothorax, secondary coagulopathy and hepatic encephalopathy – III. MELD was 38. In inpatient ward his condition become worse as marked dyspnea, itching, ascites, oliguria. The total bilirubin increasedto critical levels (571 mcmol/L), hepatocellular, kidney (Cre 220mcmol/L) and respiratory failure progression and growing of ascites tense. MARS-therapy was ineffective. Despite significant coagulopathy, the continuous renal replacement procedure was performed safely and without incident. Cadaveric donor liver transplantation was indicated and performed by standard method.

Results: In postoperative period intensive care and triple immunosuppression therapy (calcineurin inhibitor started on the 4th day, because of HRS) were done. In our patient, our treatment strategy resulted in resolution of ascites and edema, and improvement of renal function and hemodynamics. Patient discharged after 42 days after transplantation operation.

Conclusions: Thus, in this emergency case just organized and undertaken by highly qualified emergency medical care to a patient in a terminal state would save lives.

Keywords: Liver, Transplantation, Emergency indication, Hepatorenal syndrome

PE-318

Machine-Learning Models to Predict Tacrolimus Dosage in Liver Transplant Recipients

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Aims: Tacrolimus is the most widely used immunosuppressive agents to prevent rejection after solid organ transplantation. However, the use of tacrolimus should be cautious due to its narrow therapeutic index Machine learning techniques could

be good modality to decide optimal dosage of tacrolimus, compared with traditional statistical models.we have implemented a new approach to find the optimal dose of tacrolimus by machine learning technique.

Methods: We retrospectively reviewed the postoperative tacrolimus levels of patients who underwent liver transplantation at the Seoul National University Hospital from March 2016 to March 2018. We implemented an artificial intelligence model predicting future tacrolimus level by tacrolimus concentrations. We investigated hyperparameters (the number of layers in the network and the number of nodes in each layer) using a grid search and found the model with the lowest validation error.

Results: A machine learning model was derived using data from the 187 patients. As a result of testing the model with 18 patients, the predicted value of the model had an error of 1.5 ug/L from the actual measured tacrolimus level. Simulating the model in random case with a calculated tacrolimus dose to ensure the next drug concentration to be within the therapeutic range, more than 95% of the final predicted tacrolimus level comes in the therapeutic window.

Conclusions: This is the first study to use machine learning models to predict optimal dosage after liver transplantation. Machine-learning model is useful to decide optimal dose of tacrolimus immediate postoperative period after liver transplantation.

PE-319

De Novo Malignancy after Liver Transplantation: A Single Center Experience

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Aims: There are many report about solid organ transplantation recipients appear to have a higher risk of malignant tumor. It caused by suppressed immune system fail to surveillance malignant transformation. De novo malignancy after transplantation is the most common cause of late mortality. The aim of the study is to describe of experiences of de novo malignancy of major liver transplantation in South Korea.

Methods: From March 1988 to March 2018. 1793 Adult liver transplantation were performed in Seoul National University Hospital. We reviewed the causes of death and de novo cancer status of these cases retrospectively.

Results: A total of 27 de novo cancers were diagnosed among the 1793 recipients. There are 12 cases in 875 hepatocellular carcinoma (HCC) cases and 15 cases in 918 non-HCC cases. De novo cancer is not main cause of death in initial 5 years period, but after 5 year follow-up, is the main cause of death after liver transplantation. The most frequent cancers developed after liver transplantation was lymphoma (25%), second is gastric cancer (18%). And de novo hepatocellular carcinoma in non-HCC cases were found in 2 cases.

Conclusions: Liver transplant recipients were at increased risk for developing de novo cancers. We should check-up cancer surveillance on these patient more strictly.

PE-320

The Impact of Extra-Anatomical Hepatic Artery Reconstruction during Living Donor Liver Transplantation on Biliary Complications and Graft and Patient Survival

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Aims: This study was designed to analyze the feasibility of extra-anatomical hepatic artery reconstruction in living donor liver transplantation.

Methods: Patients who underwent their first living donor liver transplantation at our center between January 2008 and December 2017 were reviewed. Hepatic artery reconstruction was classified as anatomical or extra-anatomical reconstruction. We compared the background characteristics and post-transplantation outcomes, including complications, biliary complications, graft survival, and overall survival. The potential risk factors for bile leakage was analyzed using multivariable logistic regression while risk factor for biliary stricture-free, graft, and overall survival were analyzed using multivariable Cox regression.

Results: Among 800 patients, 35 (4.4%) underwent extra-anatomical reconstruction while seven patients (7/35, 20.0%) experienced hepatic artery complications after the initial anatomical reconstruction and required extra-anatomical reconstruction during reoperation. Patients who underwent extra-anatomical reconstruction (n = 2/35, 5.7%) had a similar rate of hepatic artery complications compared to those who underwent anatomical reconstruction (n = 46/772, 5.9%, P = 0.699). Extra-anatomical reconstruction was a significant risk factor of bile leakage (OR = 4.167, CI 1.928-9.006, P < 0.001) along with multiple bile ducts (OR = 1.606, CI=1.022-2.526, P = 0.040), and hepaticojejunostomy. (OR = 4.108, CI=2.190-7.707, P < 0.001) However, extra-anatomical reconstruction had no statistical relationship to biliary stricture-free survival (HR=1.602, CI=0.982-2.613, P = 0.059), graft survival (HR=1.745, CI=0.741-4.109, P = 0.203), or overall survival (HR=1.405, CI=0.786-2.513, P = 0.251). Hepatic artery complications were associated with poor biliary stricture-free survival (HR=2.060, CI=1.329-3.193, P = 0.001), graft survival (HR=5.549, CI=2.883-10.681, P < 0.001), and overall survival (HR=1.958, CI=1.195-3.206, P = 0.008).

Conclusions: Extra-anatomical hepatic artery reconstruction during living donor liver transplantation was not a risk factor of biliary stricture, graft failure, or overall survival.

PE-321

Living Donor Liver Transplantation Using Right Lobe Graft from a Donor with the Left-Sided Gallbladder Anomaly

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Aims: The occurrence of left-sided gallbladder in the absence of situs inversus is a rare congenital anomaly. It is characterized by a complex liver structural abnormalities. We, herein, describe the inclusion criteria for liver donation of the potential donors with left-side gallbladder anomaly and technical modifications in performing donor hepatectomy.
Case: A 34-year-old blood-type AB Rh+ son donated right lobe (1.27% graft volume to recipient weight ratio; GRWR) to his mother (blood type B Rh+) with B-viral hepatitis and hepatocellular carcinoma.
Results: The liver with left-sided GB anomaly should meet the following criteria for successful liver donation. First, the portal vein must be a bifurcation type. It must be a bifurcation type rather than a trifurcation type.Second, the P2 and P3 must have a common trunk. This is crucial for the remnant left lobe to retain normal portal inflow after right lobe donation. Third, the volumetry of the right and left lobe should meet the usual donation criteria. That is, the GRWR of the right lobe, greater than or equal to 0.8, and remnant left liver volume over 35% of original donor liver.
Conclusions: We have shown that it is technically feasible to retrieve the right lobe liver grafts from living donor without complication. Although, the donor with this anomaly must meet above mentioned criteria for successful LDLT, and they must be meticulously evaluated in prior to the operation.

PE-322

The Effect of Downstaging by Locoregional Treatments for Hepatocellular Carcinoma beyond Milan Criteria before Living Donor Liver Transplantation

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Aims: This study aimed to assess the survival outcomes after living donor liver transplantation (LDLT) in patients beyond Milan criteria (MC) after downstaging (DS) to within MC by locoregional treatments (LRT) and to investigate the prognostic factors for HCC recurrence.
Methods: A total of 113 patients undergoing LRT before LDLT from Jan. 2010 to Dec. 2016 were enrolled. The initial tumor size and number, and alpha-fetoprotein (AFP) before LRT and at the immediate pretransplant periods were examined.
Results: The thirty-one patients beyond MC treated with LRTs resulted into DS group (n = 8) and non-downstaging (non-DS) group (n = 23). There were no significant differences related to the type and number of LRT. The 1-, 3-, and 5-year HCC recurrence-free survival (RFS) estimates of DS group were superior to those of non-DS group (100%, 100%, and 87.5% vs. 54.8%, 49.3%, and 37%, $P = 0.028$). In a regression model predicting DS, the HCC with the lower initial number (odds ratio [OR]: 0.54, $P = 0.036$) and initial log AFP (OR: 0.53, $P = 0.048$) before LRT tended to downstage. Multivariate predictors of posttransplant recurrence were initial tumor largest size (hazard ratio [HR]: 1.20, $P = 0.025$), initial tumor number (HR: 1.11, $P = 0.101$), and immediate pretransplant log AFP (HR: 2.38, $P = 0.002$).
Conclusions: The DS may lead to favorable RFS after LDLT. The lower initial tumor size and number before LRT, and initial and immediate pretransplant AFP can corroborate a better prediction of DS by LRT and RFS after LDLT.

PE-323

Effect of Internal Stent Insertion in Duct-to-Duct Biliary Reconstruction to Reduce Bile Duct Complication in Living Donor Liver Transplantation

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Aims: Biliary complication is still considered to be a technical "Achilles´ heel" of living donor liver transplantation (LDLT) due to the high incidence, requiring long-term interventional treatment, and potential risk for graft failure. The purpose of this study was to evaluate the effectiveness of internal stent for duct-to-duct anastomosis in LDLT.
Methods: From December 2016 to October 2018, LDLT was performed in 91 patients in our center. Duct-to-duct anastomosis was performed in all LDLT patients. Ninety-one patients were divided into non-stent group and stent group according to presence or absence of internal stent. Biliary complications were diagnosed as anastomosis leakage and anastomosis stricture when interventional treatment was required.
Results: Biliary complications occurred in 20 (22.0%) patients and anastomosis site leakage occurred in 5 (5.5%) patients. Of the 91 patients, non-stent group was 48 (52.7%) patients and stent group was 43 (47.3%) patients. Anastomosis site leakage was higher in the non-stent group (n = 4, 8.3%) than in the stent group (n = 1, 2.3%), although there was no statistical difference ($P = 0.21$). Biliary complications were also higher in the non-stent group (n = 14, 29.2%) than in the stent group (n = 6, 14.0%), although there was no statistical difference ($P = 0.08$). In univariate analysis, the operation time was longer in the biliary complications group ($P = 0.04$).
Conclusions: Although there was no statistically significant

difference due to small case number, when internal stent was inserted, biliary complications including anastomosis leakage were reduced compared to no insertion. Further large-scale analyses of clinical data are required to support this study.

PE-324

Experience of Hepatic Artery Anastomosis in Living Donor Liver Transplantation Using Surgical Loupe: In Small Volume Center

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Aims: The hepatic artery (HA) reconstruction in living donor liver transplantation (LDLT) is a crucial step because of the smaller diameter of the artery and the increased risk of HA related complications. Also, any occurrence of the HA flow abnormalities in the immediate postoperative period may lead to fetal complications. Therefore, many centers use a micro-surgical technique for HA reconstruction. The aim of our study was to investigate the outcomes that HA reconstruction was performed under surgical loupe.
Methods: This study included 44 LDLTs with various end stage liver diseases at Dong-A university hospital Busan, Korea from January, 2014 to August, 2018. The medical records were retrospectively analyzed for the outcomes and HA related complications.
Results: HA reconstruction for the initial 13 LDLT surgeries was performed using a micro-surgical technique. From 14 LDLT case, HA reconstruction was performed in 31 recipients under surgical loupe with interrupted suture on posterior HA wall and running suture on anterior wall. We performed HA reconstruction in 30 adults, 1 pediatric patient (one year old) under surgical loupe, which included one dual graft LDLT. The most notable factor in surgical loupe group compared with micro-surgical group (33±5 minutes) was the quick HA anastomosis procedure with a mean time of 12±3 minutes. Fortunately, there were no HA related complications in both groups.
Conclusions: Although our case is not enough, we could consider that the HA reconstruction using surgical loupe even in smaller diameter hepatic arteries is a reliable technique and can easily be applied by an experienced surgeon.

PE-325

Hepatoblastoma: From Laparoscopic Resection to Liver Transplantation

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Aims: Introduction of liver transplantation and the application of minimally invasive surgery for selected hepatoblastoma patients made a tailored surgical approach possible according to the tumor status.
Methods: We retrospectively evaluated clinical outcomes of 38 pediatric patients with pathologically proven hepatoblastoma who underwent surgery at our institute between 2004 and 2016. Especially, we evaluated recent changes in clinical outcomes since the commencement of liver transplantations and laparoscopic resections for hepatoblastoma patients from 2013.
Results: Complete hepatic tumor resections including 5 liver transplantations were performed in all patients, with 5-year overall survival and event free survival rates of 74.8% and 73.8%, respectively. From 2013, we performed 5 liver transplantations for unresectable cases. No tumor recurrences occurred in any case after a 19.9 (14.5-35.6) months median follow-up period. Totally laparoscopic partial hepatectomies were performed (2 cases) for selected patients. Both cases showed early recovery without any complications and were free of disease recurrence after 8.1 and 19.3 months follow-up period.
Conclusions: Though long term follow-up data is necessary for validation, we suggest that an individualized surgical strategy based on the accurate evaluation of the tumor extent might improve the clinical outcomes of patients with hepatoblastoma.
Keywords: Hepatoblastoma, Liver transplantation, Laparoscopic resections, Hepatic tumor

PE-326

Chronic Renal Dysfunction Following Liver Transplantation

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Aims: With most of the immunosuppressive protocols consisting of calcineurin inhibitors (CI), nephrotoxicity has become a major long-term complication often compromising outcome.
Methods: In a single-center retrospective study, we reviewed 173 liver transplantations to identify variables indicative for the occurrence of chronic renal dysfunction (CRD) (defined as > or = 1 episode of serum creatinine increase > or = 1.8 mg/dL > or = 2 wk). Chronic renal dysfunction was found in 20 (11.7%) of all transplants [12 (7%) early (after 3-12 months), 8 (4.7%) late-onset (> 12 months)]. Compared to 5-/10-yr survival rates in non-CRD transplants (84/74%) survival was significantly decreased in early (66/46%), but unchanged in late-onset CRD (98/86%). Rates of alcoholic cirrhosis and prior renal dysfunction were significantly increased in patients with CRD. In a multivariate logistic regression analysis, only cyclosporine A (CyA) as immunosuppression remained an independent risk factor.
Results: No correlations to age, gender, rejection/retransplantation or diabetes were found. Surprisingly, renal function (creatinine) showed no difference between patients on CI monotherapy (FK/CyA) compared to those who had mycophenolate mofetil (MMF) added. In liver transplantation, early onset CRD

significantly compromises survival. CyA-based immunosuppression appears to have a stronger impact than FK.
Conclusions: The fact that patients with long-term severe chronic renal dysfunction failed to improve under MMF rescue therapy emphasizes the importance of new diagnostic strategies to earlier identify at-risk patients.
Keywords: Immunosuppressive protocols, Calcineurin inhibitors, Nephrotoxicity, Chronic renal dysfunction

PE-327

Sirolimus and Metformin Synergistically Inhibits Colon Cancer *in Vitro* and *in Vivo*

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Aims: Colon cancer has been reported as one of the frequent *de novo* cancer in Asia. However, there is no optimal treatment strategy for *de novo* colon cancer after LT. The effect of various immunosuppressants (IS) and metformin were estimated to provide the theoretical background of optimal therapeutic strategy for de novo colon cancer.
Methods: Three colon cancer cell lines (HT29, SW620, and HCT116) were used in an *in vitro* study. Furthermore, in an *in vivo* study, colon cancer models induced by subcutaneous injection of HT29 in BALB/c-nude mice. Then, the following treatments were done in both *in vitro* and *in vivo* studies, sirolimus (S), tacrolimus (T), cyclosporin A (CsA), metformin (M), metformin/sirolimus (MetS), metformin/tacrolimus (MetT), and metformin/cyclosporin A (Met CsA). Then, 3-(4 5-Dimethylthiazol-2-yl)-2 5-diphenyltetrazolium bromide (MTT) assay was performed for analysis of cell viability. Apoptosis proteins, EMT proteins, and mTOR pathway proteins were evaluated by Western blot analyses. Tumor volumes were measured for 4 weeks after inoculation.
Results: MTT-assay revealed significant cell viability inhibition in all three colon cancer cell lines in groups of S, M, and Met/S. Of note, group Met/S showed synergistic effect compare to M or S group in *in vitro study*. Western blot analysis showed significantly low levels of all investigated proteins in groups of S and Met/S in both *in vitro* and *in vivo* experiment. Tumor growth was significantly inhibited only in the Met/S group.
Conclusions: Combination of metformin and sirolimus had the most potent inhibition in the evaluated colon cancer cell lines *in vitro* and *in vivo*. This finding might have application for de novo colon cancer.
Keywords: Liver transplantation, immunosuppression, metformin, sirolimus

PE-328

First 4-Year Experience of Living Donor Liver Transplantation

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Aims: At present, living donor liver transplantation (LDLT) provides life-saving therapy for many patients who would otherwise die awaiting a cadaveric organ. LDLT has been shown to be a clinically safe addition to deceased donor liver transplantation (DDLT) and has been able to significantly extend the scarce donor pool. As long as the donor shortage continues to increase, LDLT will play an important role in the future of liver transplantation. To analyze the initial experience of LDLT at Aktobe Medical Center (AMC), Kazakhstan, in the period 2016-2019 years. All LDLT cases were performed with the participation of specialists from SHUH.
Methods: LDLT were done after the candidates (living donor and recipient) were evaluated following our practices guidelines. After donor right hepatectomies TNK solution with heparin was used for graft perfusion. "Middle hepatic vein" reconstruction performed by synthetic vascular graft. During recipient hepatectomy used "High Hillary Dissection" method. Right liver graft implantation made as a standard technique. Before portal reperfusion, liver graft washed by 5% Albumin solution. Immunosuppressive therapy in all patients included three components (CNI + MMF + Steroid) with the introduction of intravenous Basiliximab (first and fourth postoperative day).
Results: In Aktobe Medical Center were performed 11 living donor liver transplantation. Our donors' age was between 22 and 48 years. In all cases, we used the right lobe of the liver. Three cases were performed using 3D-laparoscopy. All donors discharged at 7th day after the operation. There was no complication on liver donors. Mortality was in 1 recipient, due to infection complications (cholangiogenic abscess, sepsis).
Conclusions: LDLT in Kazakhstan gives a chance to survive for patients with end-stage liver disease. Our transplant program needs to be gain experience, particularly with respect to donor selection, preoperative preparing of the recipient.
Keywords: Liver transplantation, Living donor

PE-329

Liver Transplantation during Unresitable Liver Alveokokkoz

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Aims: The purpose of the study is to evaluate the immediate and long-term results of liver transplantation in patients with unresectable alveococcosis of the liver.
Methods: 3 liver transplants to patients with unresectable liver

alveococcosis were performed at the Regional Medical Center in Kyzylorda from 2016 to 2018. 3 patients underwent related liver fragment transplantation (in all cases - the right lobe of the liver), 1 patient received a liver transplant from a post-mortem donor. In 2 patients (72.7%) there was a parasitic invasion of the inferior vena cava. All operations were performed in the variant R0. Plasticity of the great vessels when it was impossible to perform autoplasty was performed using synthetic PTFE conduits.

Results: The operation duration was 430 (390–480) min, the volume of intraoperative blood loss was 1500 (1300–2200) ml, and the duration of cold ischemia was 30 (25–45) min. The overall incidence of postoperative complications reached 45.4%, the main ones were biliary complications. Hospital mortality was 4.5%. The postoperative period lasted 20 (15–23.5) bed-days. Remote survival was 100%. The maximum observation period was 58 months.

Conclusions: Liver transplantation with resection and grafting of the great vessels, including resection of the inferior vena cava and even the right atrium, can serve as the only radical method of treating unresectable alveococcosis of the liver, allowing for satisfactory immediate and long-term results of surgical treatment in seemingly "doomed" patients. These interventions should be performed exclusively in highly specialized centers with a developed program of surgical hepatology and liver transplantation.

Keywords: Liver, Transplantation, Alveokokkoz

PE-330

Renal Safety of Entecavir and Tenofovir with Hepatitis B Immunoglobulin in Liver Transplant Patients

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Aims: Combination of potent nucleos(t)ide analougues (NAs) and hepatitis B immunoglobulin is recommended after liver transplantation for the prevention of hepatitis B virus (HBV) recurrence. Despite its proven efficacy, renal safety of NAs in liver transplant recipients has not been well defined. We aimed to assess the impact of entecavir and tenofovir on glomerular and tubular function.

Methods: We analyzed 201 liver transplant patients treated with entecavir (n = 122) or tenofovir (n = 79) with hepatitis B immunoglobulin between 2012 and 2016. Serum creatinine, phosphorus, and uric acid were measured, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Proximal tubular dysfunction was defined as the combination of hypophosphatemia (< 2 mg/dL) and hypouricemia (< 2 mg/dL).

Results: Mean eGFR at start of NAs after liver transplant was 100.8 for entecavir, 102.7 mL/min/1.73 m^2 for tenofovir group (P = 0.554). Mean eGFR at the last on-treatment visit was 80.0 for entecavir and 82.5 mL/min/1.73 m^2 for tenofovir group (P = 0.491). During the 28 months of median follow-up, 30 patients experienced decrease of eGFR < 30 mL/min/1.73 m^2 (20 [16.4%] of entecavir and 10 [12.7%] of tenofovir group, P = 0.468). Serum phosphorus and uric acid in both groups were statistically not significant at start of NAs. A total of 37 patients developed renal tubular dysfunction (11 [9.0%] of entecavir and 26 [32.9%] of tenofovir group, P < 0.001). Tenofovir (HR, 5.24; 95% CI, 2.25-12.19; P < 0.001), decrease of eGFR < 30 mL/min/1.73 m^2 (HR, 4.44; 95% CI, 1.67-11.85; P = 0.003), and use of mTOR inhibitor (HR, 2.31; 95% CI, 1.04-5.11; P = 0.04) were independent risk factors for proximal tubular dysfunction.

Conclusions: The effect of tenofovir on glomerular function was comparable to that of entecavir in liver transplant patients. However, tenofovir increased the risk of proximal tubular dysfunction. Longitudinal studies are needed to assess the long-term outcomes.

Keywords: Hepatitis B virus, Tenofovir, Renal toxicity, Liver transplantation

PE-331

Acquired Hyponatremia in Pediatric Living Donor Liver Transplantation

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Aims: The aim of this study was to evaluate the incidence of acquired hyponatremia (AH) in our pediatric living donor liver transplantation (LDLT) patients, and to identify the potential predictive risk factors of the causes of AH.

Methods: The 25 pediatric LDLT patients were divided into 2 groups: serum sodium level at the end of the surgery lower than 130 mEq/L in GI (n = 2) and higher than 130 mEq/L in GII (n = 23). Patients' data were analyzed by Mann-Whitney U test, univariate analysis, and multiple binary logistic regression model. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the logistic model formulated. P value <0.05 was regarded as statistically significant.

Results: In the multiple binary logistic regression model, the hypotonic solution administration rate (ml/kg/h) was the only independent predictor of AH with a P < 0.017. Receiver operating curve (ROC) analysis indicated that giving more than 3.5 ml/kg/h hypotonic solution infusion may cause AH. Preoperative hyponatremia did not increase the incidence of acquired hyponatremia.

Conclusions: Increasing the administration of hypotonic solution by 1 ml/kg/h in pediatric LDLT would increase the risk of developing AH by 1.272 times. The critical administration rate of hypotonic solution was 3.5 ml/kg/h.

Keywords: Hyponatremia, Pediatric living donor liver transplantation, Hypotonic solution, Arterial hypertension

PE-332

Initial Experience of Laparoscopic Right Lobectomy after Portal Vein Embolization

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Aims: Portal vein embolization is a technique used before hepatic resection to increase the size of remnant liver after surgery. This therapy redirects portal blood to segments of the future liver remnant, resulting in hypertrophy. The purpose of this study was to find out the safety and feasibility of laparoscopic right lobectomy after portal vein embolization.

Methods: All consecutive cases of laparoscopic right lobectomy after portal vein embolization between July 2014 and April 2018 in a tertiary referral hospital were enrolled in this retrospective cohort study. All surgical procedures were performed by one surgeon. There were 14 cases of laparoscopic right lobectomy after portal vein embolization. The group was analysed in terms of donor demographics, preoperative data, postoperative outcomes.

Results: The mean age of the donors was 51.3 ± 6.7 years, the gender ratio for men and women was 18:96. The mean operative time was 402.5 ± 78.8 minutes and mean postoperative hospital stay was 10.1 ± 1.7 days. The number of complications was 6 cases (5.3%) and among them, the Clavien-Dindo classification III or higher complication was 2 (1.8%). There were no mortality cases.

Conclusions: Minimal invasive living donor right hepatectomy was a safe and feasible procedure for donors. It showed an acceptable incidence of complications. The authors suggest that minimal invasive living donor right hepatectomy could be a reasonable operative option for donors in terms of cosmetic effect.

PE-333

Analysis of Cancer Incidence after Liver Transplantation in Korea Using Big Data

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Aims: Solid organ transplantation is the lifesaving procedure for patients with end organ diseases. The occurrence of malignant diseases is common after organ transplants, which affect postoperative outcomes.

Methods: We used NIH database and HIRA database for analysis. The study population was comprised of cancer-free 3,822 liver recipients between Jan 2007 to Dec 2015. Standardized incidence ratio (SIR) of cancer using indirect standardization was calculated. Cancer incidence in liver recipients were compared with Korean general population in same time from the Korea Central Cancer Registry, with SIR using indirect standardization.

Results: Compared with general population, the SIR of all cancer was 3.43 in male and 2.30 in female in liver recipients. In male patients, the SIRs for Kaposi sarcoma, non-Hodgkin's lymphoma, myeloid leukemia, and skin cancer and in female patients those for non-Hodgkin's lymphoma and liver cancer were prominent. The SIRs of non-Hodgkin lymphoma were prominent in those aged 0-39 group.

Conclusions: In conclusion, the incidence of cancer in liver transplant recipients was 2 to 3-fold higher than general population. The commonly incident types of cancer were different from the general population with higher SIR for non-Hodgkin lymphoma, Kaposi sarcoma, skin cancer, leukemia. Especially increased risk for overall cancer and non-Hodgkin lymphoma in young recipients was notable. Better knowledge of the specificities of liver recipients with de novo cancer is required to improve care in solid organ recipients. This study showed important considerations for strategies in cancer screening and surveillance in liver recipients for improvement of outcomes.

PE-334

3D-Laparoscopic Living Donor Hepatectomy: First Experience in Kazakhstan

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Aims: To date, the liver transplantation is the only radical treatment for patients with terminal stage of liver diseases. The use of live donors to some extent allowed to solve the problem of shortage of the donor organs. In the world, most donors undergo traditional open hemihepatectomy. In recent years, more and more often, a part of the liver has been withdrawn from living donors with the use of laparoscopic techniques. In the CIS countries, this technology is only being introduced. The aim of this report is to provide the first experience in implementing 3D-laparoscopic hemihepatectomy from living donors for transplantation in Aktobe Medical Center («AMC») and in the Republic of Kazakhstan

Methods: In AMC, 12 liver transplantations have been performed since 2016, 11 of which are from living donors, 1 – from a cadaveric donor. All liver transplantation operations from live donors were conducted with the direct participation of specialists from the Seoul National University Hospital. Of 11

LDLT 4 donor operations were performed using a 3D-laparoscopic technique. In all 4 cases, right-sided hemihepatectomy was performed.

Results: The average duration of an organ harvesting operation was 249 minutes. The total blood loss averaged 332.5 ml (most of the blood loss is due to the depositing of blood in an extractable liver lobe). There were no near and late postoperative complications on Clavien-Dindo Grade II were observed at donors. Patients after laparoscopic hemihepatectomy experienced a need for anesthesia only during the first day, intensified on the first and second days after the operation. Donors were discharged in 9-14 days after surgery (considering the first experiments on donor hemihepatectomy).

Conclusions: 3D technique used for laparoscopic removal of part of the liver has significant advantages compared with the traditional open surgery. With the 3D endoscopic method, a wider and more complete control of the entire surgical area and precisely detailed visualization of the anatomical structures are carried out. This technique minimizes damage to small structures of organs and tissues, which is especially important in the presence of anatomical variations. 3D laparoscopic hemihepatectomy in a living donor is less traumatic compared with the traditional open surgery. Also, this significantly reduces the volume of blood loss and the postoperative period, significantly reduces the risk of wound complications and reduces the period of full rehabilitation of patients

Keywords: Liver transplantation, 3D-laparoscopy

PE-335

Transforming Growth Factor β1 in Children of Early Age with Liver Transplantation

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Aims: Transforming growth factor β1 (TGF-β1) plays a key role in the development of the immune response, as well as in the process of liver regeneration. Measuring the level of TGF-β1 may have important clinical implications in liver transplantation, because cytokine concentration in the tissue and in blood plasma varies with different liver diseases. Aim. To analyze the dynamics of TGF-β1 levels in children-recipients with liver transplant from related donors, including from incompatible blood groups.

Methods: The study involved 12 children aged 3 to 72 months, with liver cirrhosis, developed as the result of congenital and hereditary diseases of the hepatobiliary system. All patients underwent transplantation of the left lateral liver sector from living related donors. The concentration of TGF-β1 was determined by enzyme immunoassay method in blood plasma samples.

Results: Average level of TGF-β1 in blood plasma of children with liver cirrhosis, developed as the result of congenital and hereditary diseases of the hepatobiliary system was 5,2 ± 5,5 ng/ml. A month after liver transplantation from a related donor level of TGF-β1 in blood plasma of recipients increased to 8,1 ± 9,6 ng/ml. One year after transplantation, the average level of TGF-β1 in the recipients of liver fragment was 7,7 ± 8,4 ng/ml. No association between TGF-β1 level in a month and a year after transplantation and the compatibility of the recipient with AB0 donor was found. A correlation between level of TGF-β1 prior to transplantation and the development of graft dysfunction was observed: in recipients with graft dysfunction cytokine level prior to surgery was lower than in other recipients.

Conclusions: Liver transplantation leads to a significant increase in the level of TGF-β1 in the blood plasma of children and that level is not different in recipients after transplantation of a liver fragment from AB0-compatible and AB0-incompatible donors.

Keywords: Growth factor, Liver transplantation, Incompatible blood groups, Liver cirrhosis

PE-336

Dynamics of Insulin-like Growth Factor-1 (IGF-1) in Children after AB0-Incompatible Liver Transplantation

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Aims: It is shown that liver transplantation (LT) from donor with incompatible blood type (AB0i) may be effective and safe, but the impact of such operation upon the various systems of the body has not been investigated yet. Insulin-like growth factor-1 (IGF-1) is synthesized in the liver and mediates the action of growth hormone. The level of IGF-1 is a marker of the processes of cell proliferation and tissue regeneration.

To evaluate levels of IGF-1 in children-recipients with liver transplant from AB0i (incompatible) and AB0c (compatible) donors.

Methods: 12 children aged 3 to 36 with congenital diseases of the hepatobiliar system. All patients underwent transplantation of left lateral liver sector from living related donors. The concentration of IGF-1 was determined by ELISA using specific kits in samples of blood plasma, which were received up to a month and a year after a liver transplant.

Results: Average level of IGF-1 21,0 ± 29,5 μg/l in patients before LT was significantly lower than in healthy children and did not vary in children, having received later a piece of liver from a compatible donor and from donor AB0i. In patients with anti-A/B prior to surgery average level of IGF-1 was not different from that of the patients without antibodies. One month after LT level of IGF-1 has increased both in the general group, and in patients with AB0c and AbB0i liver. The level of IGF-1 was not varied in the group with antibodies and without them.

Conclusions: The results of our studies have shown that restoration of the level of IGF-1 is not dependent on transplantation of compatible or incompatible blood type liver, as well as on the availability of anti-group antibodies.

Keywords: Insulin-like growth factor-1, Liver transplantation, Incompatible blood type, Anti-group antibodies

PE-337

Correction of Extrahepatic Portal Hypertension in Pediatric Patient after Liver Transplantation

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Aims: Liver transplantation is a multi-component and complex type of operative treatment. Patients undergoing such a treatment sometimes are getting various complications. One of these complications is a portal hypertension associated with portal vein stenosis.

Methods: In 3 years after the left lateral section transplantation from living donor in a pediatric patient the signs of portal hypertension were observed. Stenosis of the portal vein was revealed. Due to this fact percutaneous transhepatic correction of portal vein stenosis was performed.

Results: As a result of the correction of portal blood flow in the patient a positive trend was noted. According to the laboratory and instrumental methods of examination the graft had a normal function, portal blood flow was adequate. In order to control the stent patency Doppler ultrasound and MSCT of the abdominal cavity with intravenous bolus contrasting were performed. Due to these examinations the stent function was good, the rate of blood flow in the portal vein due to Doppler data has reached 80 cm/sec, and a decrease of the spleen size was noted.

Conclusions: Diagnosis and timely detection of portal vein stenosis in patients after liver transplantation are very important for the preservation of graft function and for the prevention of portal hypertension. In order to do that, ultrasound Doppler fluorimetry examination needs to be performed to each patient after liver transplantation. In cases of violation of the blood flow in the portal vein CT angiography performance is needed. Percutaneous transhepatic stenting of portal vein is a minimally invasive and highly effective method of correction of portal hypertension. Antiplatelet therapy and platelet aggregation control are the prerequisites for successful stent function.

Keywords: Portal hypertension, Liver transplantation

PE-338

Portal and Arterial Flushing with HTK and Tacrolimus Can Attenuate the Incidence of Early Liver Allograft Dysfunction

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Aims: It was shown that Tacrolimus (Tac) can suppress infl ammation and immune response involved in liver ischemia-reperfusion injury (IRI). Aim. We hypothesize that back-table arterial and portal liver perfusion with Tac can infl uence the incidence and severity of early allograft dysfunction (EAD). A prospective randomized study was conducted.

Methods: Criteria of the inclusion: First liver transplantation from DBD donor with sequential portal-arterial reperfusion. At back-table portal vein and hepatic artery were perfused each by 500 ml of HTK solution containing 20 ng/ml Tac during 10–15 min followed by portal fl ushing with 200 ml 5% solution of Albumin containing 20 ng/ml Tac and by resting of liver in effl uent. No Tac was added in the control group. Primary Outcome: EAD and severe EAD.

Results: No difference was found between groups (main vs. control) in terms of MELD (16 vs. 16), steatosis (10 vs. 10%), ballooning (45 vs. 40%) of liver grafts, recipient age (50 vs. 50 y.o.), warm ischemia time (50 vs.50 min) and total ischemia time (482.5 vs. 485.0 min). Median donor age was higher in the main group (44.5 vs.39.0 y.o.). The overall rate of EAD was 27.9%. EAD rate was significantly lower in the main group (6/43 vs.18/43; $P = 0.003$). The rate of moderate-to-severe EAD was lower in the main group (1/43 vs. 10/43; $P = 0.009$). The median levels of AST and ALT in 24 h after reperfusion were significantly lower in the intervention group (1004 vs. 1596; $P = 0.03$ and 449 vs. 759; $P = 0.057$).

Conclusions: Portal and arterial back-table liver perfusion with HTK solution with Tacrolimus may contribute to lower EAD incidence and severity.

Keywords: Tacrolimus, Liver transplantation, Portal liver perfusion ischemia-reperfusion injury, Allograft dysfunction

PE-339

A Learning Curve for Living Donor Liver Transplantation

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Aims: The number of living donor liver transplantations performed has increased rapidly in many transplant centres. However, the impact of the transplant centres' experience and learning on the transplant outcomes are not well established. Aim of the study was to evaluate the learning curve for living donor liver transplantation in our centre.

Methods: Data from 156 recipients and 156 donors who underwent surgery were reviewed. Intraoperative data and postoperative outcomes of both donors and recipients were retrospectively analysed. Recipients and donors were divided into three groups that consisted of 52 consecutive cases each.

Results: Surgical duration and intraoperative blood loss during donor surgery were decreased significantly between the earlier and the more recent cases (423±39 vs. 400±44 min and 959±523 vs. 731±278 mL, respectively; $P < 0.01$). Rates of postoperative complications and functional changes were not statistically different amongst the three donor groups. Immediate complication rate of the first 52 recipients was higher than those of the second and third cohorts. Long-term survival rates of the three recipient groups were similar.

Conclusions: The learning curve greatly influenced immediate

outcomes of recipients during the early transplant period. However, it had little influence on donor outcome; long-term outcome improvement of recipients did not depend on the accumulation of experience alone.

Keywords: The learning curve, Recipients and donors, Statistically different amongst the three donor groups

PE-340

Pediatric Liver Transplantation UMC, Kazakhstan

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Aims: Living donor liver transplantation has become a cornerstone for the treatment of children with end-stage hepatic dysfunction, especially in Kazakhstan with low rates of organ from deceased donors. In our center, 8 pediatric living donor liver transplantations we carried out since 2014. Patients between the ages of 0 to 5 years. The indications for liver transplantation in our patients were biliary atresia.

Methods: The mean hospitalization time of our patients was 25 days and the mean stay in the intensive care unit was 8 days. The Child-Pugh score was C in 2 of our patients, B in 5 patients, and A in 1 patient. The donor age ranged from 27 to 41 years, and the weight ranged from 62 to 78 kg, mothers being the donors in a majority of these. As most children require only a left lateral segment graft, the morbidity and risks to the donor are much less than those donating their right lobes. Living donor transplants are ideally suited to children as it allows for a planned procedure, allows for a near optimal size graft for the child, reduces the risk for the donor, and the incidence of rejection is reduced.

Results: The main complications after pediatric liver transplantation were infections and surgical complications including (biliary complications). We encountered biliary complications in 2 of the 8 patients and we performed surgical revision due to anastomosis leakage in 1 patient. Our immune suppression protocol is based on a combination of steroid and tacrolimus. MMF is also used as a second maintenance agent in addition to tacrolimus in children who have had a documented rejection episode.

Conclusions: Infections and biliary complications were the most common outcome occurring in children after LT. Advances in post-transplant care and monitoring of the recipients, technical refinements enable the better results.

Keywords: Pediatric, Liver, Transplantation, Billiary atresia

PE-341

Cost Prediction in Liver Transplantation Using Pretransplant Donor and Recipient Characteristics

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Aims: Liver transplantation is a costly procedure and its cost is likely driven by both donor and recipient factors. Recently, the recipient model for end-stage liver disease (MELD) score has been correlated with increased posttransplant cost; however, other factors have not been identified. We sought to identify if other donor and recipient factors are associated with increased cost.

Methods: One hundred sixty-six liver transplants performed at our center from January 2004 through February 2006 were included in the estimation sample, and the subsequent 75 transplants were used as a validation cohort. To determine whether donor factors influenced cost, two latent class linear regression models were created from the estimation sample: one considering only recipient variables (model A) and a second incorporating both donor and recipient factors (model B). The resultant models were then validated in the second group of patients and compared with the best single-segment linear regression models.

Results: Model A predictors include pretransplant intensive care unit (ICU) stay, age x body mass index, and calculated MELD. In model B, significant predictors are calculated MELD, age, age x pretransplant ICU stay, and donor age more than 40 as significant variables. In validation, only model A remained predictive of cost.

Conclusions: Although marginal donor factors are recognized to influence clinical outcome, they did not factor significantly in cost modeling. In addition to MELD, the recipient factors of pretransplant ICU stay, age, and body mass index are pretransplant variables correlated mostly with posttransplant cost across broad populations.

Keywords: Costly procedure, A remained predictive of cost

PE-342

Initial Experience of Liver Transplantation

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Aims: The aim is the presentations of results of first 3-years' experience of liver transplantation at Aktobe Medical Center (AMC). Living donor liver transplantation was performed with the specialists of SNUH specialists.

Methods: In AMC performed 12 liver transplantations: 11 – from living donor, 1 – from a cadaveric donor. LDLT were done after evaluating following our practices guidelines. After donor right hepatectomies (or liver from a cadaver) TNK solution with heparine was used for graft perfusion. "Middle hepatic vein" in living donor right liver reconstructed by synthetic vascular graft in all cases. During recipient hepatectomy used "High Hillary Dissection" method. Liver graft implantation made as a standard technique. Before portal reperfusion, liver graft washed by 5% Albumine solution. Immunosupressive therapy in all patients included three components (CNI + MMF + Steroid) with intravenous Basiliximab (1st and 4th postoperative day).

Results: Our donor's age was between 22 and 48 years. In all cases removed right lobe. For 4 donors we used 3D-laparoscop-

ic right hepatectomy. All donors discharged at 7th–10th day after the operation. There was no complication on liver donors. Died 3 recipients in the early postoperative period, and 3 patients in the late postoperative period (2 – cholangiogenic abscess with sepsis and 1 – Alcoholism with chronic rejection).

Conclusions: Liver transplantation gives a chance to survive for patients with end-stage liver disease. Our transplant program needs to be gain experience, particularly with respect to donor selection, recipients thorough preoperative preparing.

Keywords: Liver, Transplantation, Cadaver, Living donor

PE-343

Long-Term Outcome of the Rendezvous Technique in Patients with Severe Biliary Anastomotic Stricture That Cannot Cannulate after Liver Transplantation

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Aims: The purpose of this paper is to analyze the long-term outcome of the Rendezvous technique in severe strictures through which guidewires cannot cannulate.

Methods: Between 2010 and 2017, 29 patients who underwent Rendezvous technique due to severe biliary anastomosis stricture after liver transplantation were included in the study.

Results: Twenty-nine patients who underwent the Rendezvous technique showed a 100% technical success rate. Ten patients (34.4%) required stent removal; the mean stenting period was 14.9 ± 5.6 (6.65 - 24.14) months. 19 patients were maintained without stent removal; the stent-maintaining period was 13.1 ± 8.4 (3.48-38.61) months. Two patients receiving left lobe grafts maintained the stents for 27.1 ± 16.2 months. In left lobe graft, the duct anastomosis position moves to the right posteroinferior side of the patient.

Conclusions: Our results suggest that the stenting period of the Rendezvous technique was longer in severe BAS than in cannulated ERCP cases. Especially in the left liver, the position of the duct anastomosis changed to the right posteroinferior of the patient. Thus the donor duct and the recipient duct are angulated, kinking worsens, and the stenting period becomes longer.

Keywords: Rendezvous technique, Biliary anastomosis stricture, Liver transplantation

PE-344

Prevalence of Hepatopulmanory Syndrome in Liver Transplant Candidates in the North Region of Kazakhstan

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Aims: Hepatopulmonary syndrome (HPS) is indicated for the liver transplantation in patients with End-Staged-Liver-Disease (ESLD). However the prevalence of the frequency of HPS among the liver transplant candidates (LTC) in Kazakhstan is unknown. There are three centers provide liver transplantation in Kazakhstan, and these centers are divided for three region: north, south and west. Each center has independent own waiting-list, that's why the frequency of HPS in LTC is unknown. Aim of this abstract is to share the frequency of HPS in patients who are LTC in the north region of Kazakhstan.

Methods: A cross sectional study of patients with ESLD who are LTC in North region of Kazakhstan. Patients were subjected to clinical examination, laboratory investigations, pulsoxemtry, arterial blood gas measurement (≤60%). The severity of liver disease was assessed by MELD score. The diagnostic criteria for HPS were low saturation (SpO_2 ≤80%), significantly lower PaO_2, dyspnoea, platypnoea and features of portal hypertension were significantly more common in the HPS group.

Results: 70 LTC patients were enrolled in the study. 4 patients (5.7%) fulfilled the criteria for diagnosis of HPS, 3 of them female and 1 male patients. Patients with HPS showed older ages, longer duration of liver diseases, which were more severe (MELD score). Dyspnoea, cyanosis, clubbing, platypnoea, spider naevi and features of portal hypertension were significantly more common in the HPS group. In the recumbent position; patients with HPS had a significantly lower PaO_2 and showed a further fall in their PaO_2 on sitting up (orthodeoxia). One patient successfully underwent liver transplantation from cadaveric donor.

Conclusions: The prevalence of HPS among the studied group of Kazakhstan in north region liver transplant candidates is 19%. Cyanosis, clubbing, spider naevi and platypnoea–orthodeoxia are suggestive indicators of HPS. Unfortunately in our country can not provide transtoracical contrast enhanced echocardiography for patients who suspected HPS.

Keywords: Hepatopulmonary syndrome, Liver transplantation, Liver cirrhosis, PaO_2

PE-345

Splenic Artery Steal Syndrome after Liver Transplantation

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Aims: SASS is a pathological condition complicating in 1-4% of cases after OLT. It manifests itself in the redistribution of blood flow from the celiac trunk mainly to the splenic or gastroduodenal artery in the period from 2 to 5 days after the operation. A dangerous consequence of the SASS can be a thrombosis of

the hepatic artery. Among the late complications are the dysfunctions of the biliary system.

Methods: From 2013 to December 2018, 49 orthotopic liver transplantations were performed in NSCOT (Astana, Kazakhstan): 33 from a living donor (right lobe), 16 from a cadaveric. SASS was appeared in 8 cases (16.3%), 5 patients after right lobe living OLT, 3 after cadaveric OLT. All these patients presented with elevated liver enzyme levels, impaired graft function, or cholestasis. Duplex Doppler ultrasonography and celiac trunk angiography, showed a progressive decrease in hepatic arterial blood flow with an increasing RI and an increase in the flow rates of the portal vein and splenic artery.

Results: All this patients were treated with coil-embolization, leading to improved liver function, In the 3 patient result was achieved at the first attempt, the 5 patients needed a second embolization of the splenic artery, in one patient embolization was performed twice, after then underwent a splenectomy. From the first day after embolization, a gradual decrease liver enzymes and complete normalization on the 7th day was noted laboratory. Ultrasonography showed an increase in the rate of blood flow through the hepatic artery and a decreasing blood flow in the portal vein and splenic artery.

Conclusions: In conclusion, we recommend prophylactic ligation of the splenic artery for patients at risk of developing SASS. Post-transplant coil-embolization of the splenic artery corrected hemodynamic changes of SAS, but was associated with a significant morbidity.

Keywords: Splenic artery steal syndrome, Liver transplantation, Coil-embolization, Ultrasonography

PE-346

LOREK

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Aims: The aim was to show our first experience of liver transplantation in the conditions of the regional hospital.

Methods: The organ transplantation program at the Aktobe Medical Center (AMC) was launched in October 2014. 11 living donor liver transplantations were performed in AMC. There were 7 men, 5 women. The average age of patients was 47±12.5 years. 7 live donors underwent open (laparotomy) right hepatectomy, 4 – 3D-laparoscopic using. Etiological factor in 5 cases was the viral aetiology, in 4 – PBC, 1 case – viral hepatitis B + C, and 1 – congenital deficiency of protein C and S with portal vein thrombosis. The ratio of GRWR was 0.8 and more. Middle hepatic vein was reconstructed with a synthetic vascular stent. The average MELD score was 17.9 ± 2.7. Liver transplantation was performed according to a classical technique. Immunosuppression scheme included tacrolimus, MMF, methylprednisolone.

Results: Six patients had complications: 2 patients – postoperative haemorrhage from arterial anastomosis; 2 – biliary stricture with cholangitis; liver abscesses and development of abdominal sepsis and they had PTBD; 1 – on the background of the inconsistency of the gastric stitches (Parciori's operation), multiple sub-diaphragmatic and intertitular abscesses of the abdominal cavity developed. The average duration of the postoperative period in the recipients was 31 ± 12 days. Sixth recipients died. In the nearest postoperative period died 3 patients (progressive porto-pulmonary syndrome – 1, pancreonecrosis – 1, infectious-toxic shock – 1). Three died in the distant postoperative period (progressive cholangiogenic sepsis – 2, chronic liver rejection – 1).

Conclusions: The liver transplantation is an effective and radical method of treatment of terminal stages of chronic diffuse liver diseases. The results of the initial experience of kidney transplantation in the conditions of the regional hospital do not differ from the average results of our domestic and foreign clinics.

Keywords: Liver, Transplantation, LDLT outcome

PE-347

Hepatic Abscess after Ortotopic Liver Transplantation

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Aims: Hepatic abscess is a serious complication which may occur after liver transplantation. This abstract reveals the predisposing factors, treatment, and outcomes associated with hepatic abscess.

Methods: This abstract consist of review of all liver transplant recipients in NSCOT. From 2013 to July 2017 48 orthotopic liver transplantations were performed in in NSCOT: 33 from a living donor (all the right lobe), 11 from a cadaveric donor. Hepatic abscess was defined as a parenchymal hepatic lesion consistent with abscess (as revealed by MRCP, ultrasonography and celiac trunk angiography), positive liver or concurrent blood cultures.

Results: Of 48 liver recipients, identified 3 patients (6,9%) who had experienced 4 episodes of hepatic abscess, 24-52 days after transplant. 2 patients after LDLT (right lobe), 1 patient after DDLT. Biliary reconstruction was done by duct-to-duct in all 3 cases (TTR technique in 2 case of LDLT). The predisposing factors was: bile-to-duct anastomosis stricture in 2 case (1 case due to hepatic artery stenosis), early hepatic artery thrombosis in 1 case. In 2 case was performed PTBD: in 1 case initially performed transarterial hepatic artery stenting, then PTBD. This patient still alive; 1 patient was died from sepsis. In 1 case performed transarterial fibrinolysis for 2 days (Actilyse 10-15 mkg per 3 hours) with stenting, after 32 POD underwent re-transplantation from cadaveric donor, despite all of this treatment with broad spectrum antibiotics and antifungals patient was died.

Conclusions: Hepatic abscess is one of the main causes of morbidity after LTx that we faced. In 3 patients from 48 was occurred (6.9%), 2 patients died, 1 patient still alive. Hepatic abscess after liver transplantation may be treated successfully with percutaneous and retransplantation with broad spectrum antibiotics.

Keywords: Hepatic abscess, Liver transplantation, PTBD, Retransplantation

PE-348

Liver Transplantation for Patient with Emergency Indications

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Aims: Immunosuppressive medications have many negative effects. One way of solving this is to minimize immunosuppression.
Methods: 30 liver transplantations performed in our Medical Center between 2013 and 2018: 22 – from living donor, 8 – from the cadaver. Most liver transplants were performed in collaboration with SNUH (Seoul, Korea). The indications for liver transplantation (LT) were as follows: primary biliary cirrhosis – 6, hepatitis C virus (HCV) cirrhosis – 3, hepatitis B virus (HBV) cirrhosis – 20, autoimmune hepatitis – 1.
Results: In 28 recipients at the beginning immunosuppression was based on 3 components: Tacrolimus – MMF – Corticosteroids with Baziliximab on 1st and 4th operating days. All our patient's discontinuous steroid after 6-12 month after transplantations, depending on the aetiology of liver cirrhosis. One patient finished receiving MMF 2 years after transplantation. Two patients (after living donor transplantation) received (and receive now) only Tacrolimus and had no rejection episodes. But they have appointed hormones for a week after transplantations. One patient had a conversion from Tacrolimus to Cyclosporine. She had hyperglycemia. After conversion glucose levels returned to normal.
Conclusions: Minimization of immunosuppression is a necessary goal for transplant patients. Many immunosuppressive drugs have side effects, which lead to undesirable consequences or death. Immunosuppression minimization regimes should be safe for rejection and infectious complications in liver transplant patients.

Keywords: Liver transplantation, Immunosupression

PE-349

Immunosuppression after Liver Transplantaton

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Aims: Immunosuppressive medications have many negative effects. one way of solving this is to minimize immunosuppression.
Methods: 30 liver transplantations performed in our Medical Center between January 2016 and January 2019: 22 – from living donor, 8 – from cadaver. Most liver transplants were performed in collaboration with SNUH (Seoul, Korea). The indications for liver transplantation (LT) were as follows: primary biliary cirrhosis – 6, hepatitis C virus (HCV) cirrhosis – 3, hepatitis B virus (HBV) cirrhosis – 20, autoimmune hepatitis – 1.
Results: In 28 recipients at the beginning immunosuppression was based on 3 components: Tacrolimus – MMF – Corticosteroids. All patients discontinuous steroid after 6-12 month after transplantations, depending on the etiology of liver cirrhosis. One patient finished receiving MMF 2 years after transplantation. Two patients (after living donor transplantation) received (and receive now) only Tacrolimus and had no rejection episodes. But they were appointed hormones for a week after transplantations. One patient had a conversion from Tacrolimus to Cyclosporine. She had hyperglycemia. After conversion glucose levels returned to normal.
Conclusions: Minimization of immunosuppression is a necessary goal for the transplant patients. Many immunosuppressive drugs have side effects, which lead to undesirable consequences or death. Immunosuppression minimization regimes should be safe for rejection and infectious complications in liver transplant patients.

Keywords: Immunosuppression, Liver, Transplantaton

PE-350

Tumor Markers at the Time of Liver Transplantation: Reliable Predictors of Hepatocellular Carcinoma Recurrence after Locoregional Treatment

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Aims: Prediction of the hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) is important for clinicians to make a treatment decision. We conducted a study of 158 HCC patients underwent liver transplantation after locoregional treatment to clarify when is optimal time point to assess HCC recurrence from serum tumor maker.
Methods: We retrospectively recruited data of AFP and PIVKA-II at various time points; at the time of LT, pre-LT maximum, pre-LT minimum, maximum after last LRT. Also we found cutoffs of two markers for HCC recurrence and assessed hazard ratio (HR) of cutoffs adjusted with cancer staging on explanted pathology, Esmond grade, liver function and total number of pretransplant LRT.
Results: AFP at LT (cutoff 20 ng/mL; HR 3.67, 95% CI 1.86-7.25), maximum AFP after last LRT (cutoff 75 ng/mL; HR 2.60, 95% CI 1.36-4.99) were independently predictive for HCC recurrence. PVIKA-II at LT (cutoff 2.22 mAU/mL; HR 2.22, 95% CI 1.05-4.67), maximum PIVKA-II after last LRT (cutoff 130 mAU//mL; HR 2.38, 95% CI 1.16-4.89) were also significantly associated with HCC recurrence. Pretransplant maximum level or degree of decline of both tumor markers were not significant factors.
Conclusions: Current study demonstrated that AFP and PIVKA-II at the time of LT were reliable predictors of hepatocellular car-

cinoma recurrence after locoregional treatment regardless of maximum pretransplant values. Clinicians can rely on the current level of tumor markers at the time of LT.

Table 1. Tumor markers and hazard of HCC recurrence after liver transplantatio

Variables	Adjusted HR (95% CI)	*P*
AFP at LT > 20	3.67 (1.86-7.25)	<0.001
AFP, pre-LT max > 300	1.72 (0.90-3.31)	0.103
AFP, pre-LT min > 10	1.33 (0.60-2.96)	0.480
AFP, post-last LRT max > 75	2.60 (1.36-4.99)	0.004
AFP, pre-LT max – at LT > 200	2.06 (1.07-3.99)	0.031
Duration, AFP pre-LT max – at LT < 6 mon	1.15 (0.58-2.27)	0.688
Duration, AFP pre-LT min = at LT	3.31 (1.12-9.77)	0.030
PIVKA at LT > 65	2.22 (1.05-4.67)	0.036
PIVKA, pre-LT max > 300	1.84 (0.91-3.73)	0.090
PIVKA, pre-LT min > 20	0.99 (0.43-2.30)	0.981
PIVKA, post-last LRT max > 130	2.38 (1.16-4.89)	0.019
PIVKA, pre-LT max – at LT > 200	0.98 (0.46-2.09)	0.958
Duration, PIVKA pre-LT max – at LT	1.31 (0.67-2.54)	0.433
Duration, PIVKA pre-LT min = at LT	0.72 (0.21-2.45)	0.598

HRs were adjusted with TNM staging, Esmond grade, pretransplan meld score and the number of pretransplant LRT.

Keywords: Liver transplantation, Hepatocellular carcinoma, Tumor marker

PE-351

Splenic Artery Embolization Following Liver Transplantation: Single Center Experience

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Aims: Among complications after orthotopic liver transplantation (OLT) hypersplenism (thrombocytopenia, leukocytopenia, anemia) syndrome and ascites are not rare. Mainly this condition is indicated to open splenectomy. Although, it is well known for negative effects after splenectomy procedure. Recently, splenic artery embolization (SAE) has been reported as well-designed procedure and many centers are sharing their experience with effective results. In this report, we would like to present the early outcomes of SAE in 6 patients after liver transplantation, who had hypersplenism, ascites and uncontrolled hyperbilirubinemia.

Methods: Between January 2015 and January 2019 we performed 37 OLT: 28 from living donor (2 – left lobe, 26 – right), 9 – from cadaver. Six patients after OLT received splenic artery embolization (SAE). Before OLT 2 recipients with primary biliary cirrhosis, 4 – Hepatitis B Virus-related liver cirrhosis. Two patients after right lobe living OLT, one – cadaveric OLT. SAE in 6 cases were performed after 6 and 18 months, and just in one case it was performed soon after operation. The indications for SAE was based on clinical and ultrasonographic investigation (ascites, splenomegaly) and laboratory criteria (thrombocytopenia, when PLT<60x10^3/mm^3, leukocytopenia, when WBC<2x10^3/mm^3). 2 recipient has leuko-thrombocytopenia and refractory ascites, 1 – only thrombocytopenia, 3 – with uncontrolled hyperbilirubinemia. SAE was performed via a percutaneous femoral artery approach by interventional radiologists in operating room under local anesthesia. All patients has preoperative antibiotic prophylaxis and desensitize medication. After selective celiac and splenic arterial angiographies were obtained to determine the target splenic artery branches. Transcatheter splenic artery branches occlusion was performed by the deployment of embolic device.

Results: The size of spleen was between 8.5-12.5 cm to 17.5-22.0 cm. Patients ascites were more than 1000 ml. Total spleen embolization volume was approximately 70%. Ascites decreased after SAE in all patients. After SAE the platelets levels increased in all patients too. In one patient (who has leukocytopenia), WBS level normalized for 3 days. Uncontrolled hyperbilirubinemia decreased in 10-14 days. After SAE: 2 patients had analgesia none-needed abdominal pain, 2 – had fever (max T^o was 38.5^{o}C) during 3 days. The patients were discharged 6, 8, 9 days after SAE. One patient had perisplenic abscess without fever 1 month later after discharge. Abscess was drained under ultrasound control.

Conclusions: SAE, although limited by the minimal cases, is a safety and effective minimally invasive methods for treatment hypersplenism and ascites of recipients after OLT. Also, it is proved in patients who have immunosuppressive condition as alternatives to open total splenectomy.

Keywords: Embolization, Liver, Transplantation, Hypersplenism

PE-352

Pediatric Liver Transplantation in University Medical Center Astana

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Aims: Living donor liver transplantation has become a cornerstone for the treatment of children with end-stage hepatic dysfunction, especially in Kazakhstan with low rates of organ from deceased donors. In our center, 8 pediatric living donor liver transplantations we carried out since 2014. The indications for liver transplantation in our patients were biliary atresia.

Methods: The mean hospitalization time of our patients was 25 days and the mean stay in the intensive care unit was 8 days. The Child-Pugh score was C in 2 of our patients, B in 5 patients, and A in 1 patient. The donor age ranged from 27 to 41 years, and the weight ranged from 62 to 78 kg, mothers being the donors in a majority of these. As most children require only a left lateral segment graft, the morbidity and risks to the donor are much less than those donating their right lobes. Living donor transplants are ideally suited to children as it allows for a

planned procedure, allows for a near optimal size graft for the child, reduces the risk for the donor, and the incidence of rejection is reduced.
Results: The main complications after pediatric liver transplantation were infections and surgical complications including (biliary complications). We encountered biliary complications in 2 of the 8 patients and we performed surgical revision due to anastomosis leakage in 1 patient. Our immune suppression protocol is based on a combination of steroid and tacrolimus.
Conclusions: Infections and biliary complications were the most common outcome occurring in children after LT.

PE-353

LDLT Program University Medical Center Astana

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Aims: Liver transplantation is the only life-saving intervention for patients with end stage liver disease. LDLT donors are typically healthy adults who do not derive any medical benefit from the procedure for themselves. Donor death is the most serious complication after LDLT, with estimated mortality at 0.28 to 1.0 percent, however, the exact risk cannot be precisely quantified due to the lack of a centralized database measuring donor outcomes.
Methods: We retrospectively reviewed the medical records of 120 LDLT recipients who underwent the procedure using a right liver graft between May 1999 and September 2012 in the Department of Surgery. Donor age, sex, and the degree of hepatosteatosis were compared between the groups. Recipient age, sex, body mass index (BMI), and transplantation indications were also compared between the two groups. We measured the recipients' Child-Turcotte-Pugh (CTP) and Model for End-stage Liver disease (MELD) scores in both groups to compare the preoperative disease severity. Although the general donor age recommendation in our institution is 16-55 years of age, the donors in this study were 16-67.
Results: The anatomical structure of the vasculature and biliary tree and liver consistency were evaluated using abdominal CT, ultrasonography, and magnetic resonance cholangiopancreatography.
Conclusions: LDLT using elderly donors could induce more serious complications and higher mortality rates than those at using younger donors. As such, careful donor selection is needed, especially with regard to assessing the condition of potential elderly donor livers. Furthermore, a large-volume and multicenter study of complications and outcomes of LDLT using elderly donor liver is required.

PE-354

Early-Onset and Bad Place Post Transplantation Lymphoproliferative Disorder (PTLD) after Liver Transplantion: Case Report

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Post transplantation lymphoproliferative disorder (PTLD) is the most severe complication among liver transplantation recipients, the overall incidence rate is reported to be 1% to 4%. The Oncogenic Epstein-Barr virus (EBV) is the most important pathogenic driver in early-onset cases. Monitoring EBV deoxyribonucleic acid (DNA) loads in blood is widely used to detect PTLD early in many transplantation centers. We report a case of EBV positive (EBV+) diffuse large B-cell lymphoma (DLBCL) in a patient only 2 months after liver transplantation.
A 49-year-old male visited the transplantation center for a 2 month post-transplantation scheduled medical checkup. He was in poor general condition, also complained of an itching sense all over his body. A liver computed tomography (CT) detected a 2.1cm heterogenous mass at the hilar area of the liver and a needle biopsy confirmed the diagnosis of DLBCL. The EBV polymerase chain reaction (PCR) test level was at 25,300 copies/mL. Reduction of immunosuppression (RIS) was the first line treatment, Rituximab monotherapy followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment was repeated for six cycles.
EBV plays a key role in very early onset PTLD like this patients cases . Therefore, EBV positive transplant recipients should continuously check blood EBV PCR levels for PTLD early detection.

PE-355

Laparoscopy-Assisted Hybrid versus Open Living Donor Right Hepatectomy: A Comparison of Surgical Outcomes

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Aims: Applications of minimally invasive surgery in living donor hepatectomy (LDH) is increasingly accepted in worldwide. However so far, pure laparoscopic living donor hepatectomy has only been performed at experienced large-volume transplant centers due to the concerns over donor safety. Laparoscopy-assisted (hybrid) approach has been designed to not only provide reduced small wound but also minimize the risk of technical complexity. The aim of this study is to evaluate the safety and efficacy of our laparoscopy-assisted (hybrid) living donor right hepatectomy and compare with conventional open surgery in terms of perioperative outcomes
Methods: Between January 2013 and November 2018, total 311 Living donor right hepatectomy (LDRH) were performed at Severance Hospital. Among them, 41 robotic LDRH were excluded.

Finally, total 270 LDRH case were enrolled in this study. We divided the patients into two groups [hybrid group (n = 126)] and open group (n = 144)]. Donor characteristics, perioperative surgical outcomes, postoperative complications were retrospectively reviewed between the two groups.

Results: Total 270 LDRH were performed with zero mortality. All of the hybrid techniques were completed without any extra additional subcostal incision. Hybrid procedure was associated with a reduction in operative blood loss (258 vs 307, $P = 0.032$); shorter hospital stay (8.5 vs 10.8, $P = 0.01$) There was no significant difference between two groups in donor characteristics, the incidence of postoperative complications greater than or equal to Clavien-Dindo class III. operation time, transfusion rate, and postoperative liver function tests, recipient outcomes.

Conclusions: Donor safety is major cornerstone in living donor liver transplantation. Our experience suggests that hybrid approach in living donor right hepatectomy appears to be a safe and feasible procedure. It could be considered an alternative minimally invasive approach.

Keywords: Minimally invasive surgery, Laparoscopy assisted living donor right hepatectomy, Hybrid living donor hepatectomy, Donor safety

PE-356

Tablet or Capsule Form Combined with Tacrolimus after Liver Transplantation: A Prospective Randomized Trial

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Backgrounds: Tablet and capsule forms have advantages and disadvantages in the market. Generally, the tablet form (500 mg) of mycophenolate mofetil (MMF) is more convenient for drug ingestion and more cost-effective than the capsule form (250 mg). We examined the efficacy and safety of MMF in its different forms combined with tacrolimus in liver transplant recipients.

Methods: A randomized controlled trial was performed to compare the efficacy and safety between the tablet form of MMF (tablet group) and the capsule form of MMF (capsule group) in liver transplant patients. One hundred sixteen patients were enrolled in present study from 2014 to 2017. Fifty-six patients in the full-analysis set (FAS) population were in the capsule group and 60 were in the tablet group. The primary endpoint was incidence of biopsy-proven acute rejection (BPAR) by 24 weeks after liver transplantation (LT). Secondary endpoints were patient survival, serum creatinine level, and adverse events.

Results: In the per-protocol (PP) population, 45 patients were in the tablet group and 49 were in the capsule group. There were no statistically significant differences in MMF dose, mycophenolic acid trough level, and tacrolimus trough level between the two groups. The incidence of BPAR at 24 weeks after randomization was 6.7% in the tablet group and 6.1% in the capsule group ($P = 0.627$). All patients with BPAR responded well to steroid pulse therapy and increased tacrolimus. Serum creatine level and eGFR were not different between the two groups. The incidence of serious adverse events was 7.2% in the tablet group and 7.6% in the capsule group, and none were related to formulation. There was no significant difference in incidence of discontinuations or serious adverse events between the two groups.

Conclusion: The present study suggests that the new tablet formulation can be a useful treatment option to maintain a consistent systemic exposure level of MMF, which may help reduce graft failure in liver transplant patients.

PE-357

Splenorenal Shunt Occlusion Assosciated to Portal Vein Thrombosis after Liver Transplantation: Report of Two Cases and Literature Review

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Aim: To report and assess the outcome of splenorenal shunt (SRS) occlusion associated to portal vein thrombosis (PVT) after liver transplantation.

Background: PVT is one of complications (1-3%) after liver transplantation. It can significantly reduce graft outcome and patient survival. SRS that may divert portal blood flow to the systemic circulation, attribute to reduced hepatic perfusion, portal vein compromise and PVT.

Method: From October 2018 to February 2019, two patients who recently underwent liver transplantation presented PVT and large SRS (41/F and 58/M). Portal venography and mechanical thrombectomy were performed through trans-splenic approach. Delayed retrograde SRS occlusion were performed through trans-jugular approach using vascular plugs. Outcomes and complications were assessed by Doppler ultrasound and serum liver enzyme levels.

Result: Venography revealed total thrombotic occlusion of main portal vein and majority of flow drained throught SRS to systemic circulation. Thrombectomy was successfully performed and post-venography showed patent portal flow, but still majority of flow drained into SRS. Delayed retrograde SRS occlusion were successfully performed using vascular plugs. Follow up Doppler US or CT examination of these two patients showed patent portal vein. Liver enzymes were gradually normalized. Both patients discharged without any complication nor further treatment.

Conclusion: SRS occlusion is effective and safe procedure for portal vein compromise after liver transplantation.

Surgery, Technical Issues

PE-358

3D-Laparoscopic Surgery in Difficult Localizations of Echinococcosis Cysts of the Liver

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Aims: To improve results and reduce the trauma of surgical intervention in patients with liver echinococcosis

Methods: In our clinic, for the first time in the Republic of Kazakhstan, a 3D-laparoscopic technique was used to remove hydatid cyst in a male patient, aged 56 years. The indication to use of 3D-laparoscopy for the purpose of echinococcectomy was the inaccessible localization of the liver cyst. According to laboratory data, ultrasound and CT, the cyst was solitary, measuring up to 6.5 cm in diameter, with chitinousmembrane and located in segment 8 of the liver. Laparoscopy was performed according to standard methods under endotracheal anesthesia. We used 4 troacars– two for 12 mm and two for 10 mm. After the cyst was identified, the area of the intended puncture was covered with napkins moistened with hypertonic NaCl solution. Cyst puncture was performed with a needle, while holding the cyst wall with a clamp. After dissecting the fibrous capsule, the entire chitinous membrane of the cyst was evacuated with a vacuum aspirator. The residual cavity of the cyst was treated with a 25–30% NaCl solution with an exposure of 15 minutes. The revealed cystobiliary fistulas were coagulated. The drainagewas placed to the subhepatic space.

Results: The postoperative period was uneventful, without complications. Drainage was removed on the 3rd day after operation. Control ultrasoundwas without pathological changes. The patient was discharged on the 5th day after surgical treatment.

Conclusions: The use of 3D-laparoscopic techniques for removal of the difficult approaching cysts of the liver (7-8 segments) with strict adherence to the principle of aparasity is the most effective and promising method of surgical treatment of liver echinococcosis.

Keywords: Liver, 3D-Laparoscopic, Echinococcosis, Cystectomy

PE-359

Surgery-Related DIC Predicts the Severity of Complication after Major Hepatobiliary Pancreatic Surgery

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Aims: The rate of postoperative morbidity including infectious complications remains high after major hepatobiliary pancreatic (HBP) surgery. Although surgery-related disseminated intravascular coagulation (DIC) occurs in some cases, the significance of surgery-related DIC has not been elucidated in HBP surgery. The objective of this study was to evaluate the influence of surgery-related DIC on the severity of complications after HBP surgery.

Methods: We compared the baseline characteristics and complications among the patients with and without surgery-related DIC on postoperative day 1 (POD 1) after HBP surgery between 2010 and 2018. The severity of complications was assessed using the Comprehensive Complication Index (CCI).

Results: We analyzed the records of 100 patients with hepatectomy in two or more segments, hepatectomy with biliary tract reconstruction, and pancreaticoduodenectomy. The DIC group (surgery-related DIC on POD 1) was characterized by a longer operation time, an increased volume of blood loss, and higher levels of liver enzymes. The DIC group exhibited significantly elevated rates of surgical site infection, sepsis, prolonged intensive care unit stay, more frequent blood transfusions and higher CCI. Furthermore, surgery-related DIC on POD 1 was an independent risk factor for the development of severe complications, as indicated by a high CCI score (≥ 40).

Conclusions: Surgery-related DIC on POD 1 was an independent predictive factor for the development of severe complications after major HBP surgery.

Keywords: DIC, HBP surgery, complication

PE-360

Anterior Approach for Right Hepatectomy and Right Anterior Sectionectomy with Hanging Maneuver for Large Hepatocellular Carcinoma: A Single-Center Experience in Vietnam

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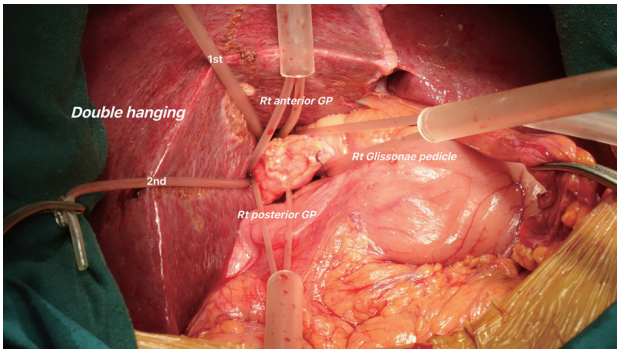
Aims: Right hepatectomy and right anterior sectionectomy for large hepatocellular carcinoma via the anterior approach without prior liver mobilization is an accepted technique and the liver hanging maneuver facilitates this procedure. Hepatic parenchymal transection remains a critical part of this operation during which excessive blood loss can occur. Control of blood loss is important in hepatectomy as excessive bleeding and blood transfusion are associated with increased postoperative morbidity/ mortality rates and compromised long term oncological outcomes in these patients.

Methods: To report the surgical and preliminary outcomes of major right hepatectomy and right anterior sectionectomy for

large hepatocellular carcinoma (HCC) using the anterior approach with hanging maneuver in single center in Vietnam. In patients who had large HCC (over 10 cm in size) at the right lobe of liver and underwent hepatic resection such as right hepatectomy or right anterior sectionectomy, the technique of anterior approach with the liver hanging maneuver was used. All consecutive patients who underwent elective right hepatectomy or right anterior sectionectomy in our center using this technique from March 2014 to July 2016 were retrospectively studied. This study aimed to describe this technique and report the preliminary outcomes.

Results: Twenty one patients with hepatitis B-related hepatocellular carcinoma (HCC) with cirrhosis underwent the technique for right hepatectomy and right anterior sectionectomy using the anterior approach with the liver hanging maneuver. The mean blood loss, liver parenchymal transection time and operation time were 280.3 ± 72.6 ml (SD), 49.3 ± 8.1 min, and 291.7 ± 58.2 min, respectively. No patients developed postoperative bleeding or bile leak. There was no 90-day mortality.

Conclusions: To achieve complete anatomic hepatectomy in a large hepatocellular carcinoma (HCC), hepatic transection through an anterior approach is required. Liver hanging maneuver is a useful procedure for transection of an adequately cut plane in anatomical liver resection. It may reduce intraoperative bleeding and transection time, and it caused no major complications and mortality.



Keywords: Hepatectomy, Hepatocellular carcinoma

PE-361

An Experience of Laparoscopic Operations in the Liver Local Lesions

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Aims: 10 laparoscopic liver resections were performed In the City Hospital of Kyzylorda (Kazakhstan) in 2018. In 3 cases, the indication for the operation were hemangiomas with a diameter of more than 5 cm, in 3 cases – solitary metastases of colorectal cancer, in 2 – focal nodular liver hyperplasia with signs of progressive growth and in 2 cases – giant true liver cysts. The aim of the study was to Choose the rational surgical access for liver.

Methods: 4 left-sided caval lobectomies, 6 atypical segmental liver resections were performed By the volume of interventions. Standard endovideosurgical equipment was used. Access is carried out through 4-5 laroport. The handle loops to perform Pringl-a maneuver taken out through a separate puncture in the right hypochondrium. Liver parenchyma dissection was performed using ultrasonic scissors and mono-and bipolar electrocoagulation. Large tubular structures were clipped. At atypical resections, as well as at the intersection of thin marginal areas of the parenchyma, endoscopic linear crosslinking devices were used to achieve hemo and cholestasis. Extensive resection of the wound surface of the liver was further processed organosilanes coagulation. In one case, a hemostatic sponge "tachocomb"was used to cover the wound surface. The drug was removed in a container through extended trocar access in the left hypochondrium.

Results: In the vast majority of cases, there were no complications in the early and late postoperative periods. The period of postoperative hospital treatment was 4-5 days. In one case, there was prolonged bile leakage through the safety drainage from the subsegmental duct. Biliary fistula was closed independently after 21 days.

Conclusions: Thus, improving the efficiency of surgical treatment of patients with focal liver formations through the use of endovideosurgical methods dictates the need for further scientific and clinical resolution of issues relating to the conditions under which laparoscopic liver resection is possible, indications and contraindications to it, as well as a number of technical aspects relating to the effectiveness and safety of methods of separation of the hepatic parenchyma.

Keywords: Laparoscopic, Liver, Resection, Technique

PE-362

Extensive Liver Resections for Alveococcosis

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Aims: to evaluate the results of extensive liver resections for alveococcosis.

Methods: For the period from April 2009 to August 2018. 398 patients with liver alveococcosis were treated. 350 patients from 398 were operated, 167 of them underwent extensive liver resections (47.7%). The average duration of inpatient stay is 16.5 ± 0.9 bed-days.

Results: 167 patients had 278 complications: mechanical jaundice - 64, cavernous forms of alveococcosis - 35, germination in neighboring organs (lung, kidney, diaphragm, stomach, pancreas, hepatoduodenal ligament, large intestine, adrenal gland) - 67, bilobar lesion - 97, MTS in lungs - 7, MTS to the brain - 3, MTS to soft tissues - 3, hepato-bronchial fistula 2. There were 167 (100%) extensive liver resections: right-sided hemihepatectomy 83 (47.3%), of which 3 were with bile duct resection, 11

were with resection of the portal vein, 5 were with resection and prosthetic IVC; left-sided hemihepatectomy - 26 (15.6%), of them with resection of the bile duct - 2, with resection of the portal vein - 4; expanded left-sided hemihepatectomies — 19 (11.4%), of them with resection of the bile duct — 1, with resection of the portal vein — 4; expanded right-sided hemihepatectomy - 43 (25.7%), of them with resection of the bile duct - 3, with resection of the portal vein - 3, resection and prosthetic IVC – 2. Postoperative complications were in 24 patients (14.3%): liver failure - 16, bile excretion - 6, reactive pleuritis - 7, bilateral pneumonia - 1, gastrointestinal bleeding - 1. Mortality is 2.4% - 2 patients.

Conclusions: The final decision on resectability can be made after intraoperative revision, IOUS, USDG and liver mobilization, liver resection is quite feasible even with invasion into the main vessels (PV, IVC,) and bile ducts (hepaticoholedochus), R0 liver resection remains a radical method of treatment.

Keywords: Liver resections, Alveococcosis, IVC, Portal vein

PE-363

The Liver Alveococcosis Surgeries with Inferior Cava Vein and Portal Vein Invasions

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Aims: to evaluate the results of surgical treatment of the liver alveococcosis with the IVC and portal vein invasions.

Methods: We analyzed the results of treatment of 220 patients with liver alveococcosis for the period from April 2009 to March 2015. All these patients received treatment in The Surgical Gastroenterology and Endocrinology Department of the National Hospital under the MoH of the Kyrgyz Republic. In 48 (21.8%) patients, alveococcosis was sprouted to the IVC and caval gates and portal vein, depending on that patients were divided into two groups with lesions of the IVC and the portal vein. The average age was 35.8+\- 11.4 years. The ratio of males / females is 18/30.

Results: The first group included 32 (66.7%) patients, the second group included 16 (33.3) patients. In the first group, the percent of radical liver resection was 8.3%, in the second – 27%. The following types of operation were performed with circular resection of portal vein and marginal resection of the IVC: ERHHE – 11 (1st group – 8, 2nd group – 3) RHHE -15 (1st group – 7, 2nd group – 8), ELHHE – 6 cases (1st group – 2, 2nd group – 4), LHHE – 3 cases (1st group – 2, 2nd group – 1), non-radical resections – 5, explorative laparotomy – 6 cases. The blood loss during the operation varied from 200 ml to 3000 ml. The minimum duration of the operation is 1 h., the maximum is 9h 30 min.

Conclusions: Despite of the invasive growing up of the alveococcal mass to the main vessels, IVC and portal vein, it is possible to perform radical surgery. According to our data, the percentage of radical liver resections in the cases of the portal vein invasion is higher (27%) than in the invasion of the IVC (8.3%).

Keywords: Inferior cava vein, Liver alveococcosis, Portal vein, Invasions

PE-364

The Liver Alveolar Echinococcosis Surgery of Children

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Aims: Analysis of the results of surgical treatment of alveococcosis of children.

Methods: From April 2009 to November 2017, 24 children with alveococcosis of the liver aged from 7 to 18 years had a treatment in the Department of Surgical Gastroenterology and Endocrinology of the National Hospital under the Ministry of Health of the Kyrgyz Republic, in the Department of Surgery No.1 of the National Center for Pediatrics and Pediatric Surgery. There were 12 boys and 8 girls. The patients were divided according to the PNM classification: P1N0M0 - 12, P3N0M0 - 2, P1-3N1M0-6, P4N1M0-4, According to the chart. 50% of children were diagnosed to have liver alveococcosis in an advanced stage, when adjacent organs and great vessels and tubular structures of the liver gate are affected. There were complicated forms as follows: mechanical jaundice - 2, cavernous forms of alveococcosis - 4, germination in neighboring organs and great vessels - 8, bilobar lesion – 2.

Results: 18 (90%) liver resections were performed on patients with liver alveococcosis. Extensive liver resections - 8, three of them segments resection - 1, RHHE - 4, RHHE with atypical resection S III - 1, ELHHE -2. Atypical liver resections - 10 of them are segmentectomy - 9 and bisegmentectomy – 1. The maximum blood loss was 1200 ml, the minimum was 200 ml. 13 (65%) patients were operated radically. Palliatively7 (35%) patients, 2 of them percutaneous transhepatic cholangiostomy. Postoperative complications occurred in 2 (10%) patients in the form of bile leakage.

Conclusions: Rural residents more often get sick with this disease, and town speople who are engaged in hunting and members of their families. A high percentage of complicated forms of the disease among children is 50%, which requires carrying out seasonal at least twice a year, household rounds and instrumental research methods (ultrasound) of children and adults from unfavorable regions of the Republic for early diagnosis of alveococcosis. The only and radical method of treatment is liver resection within healthy tissues.

Keywords: Alveococcosis of children, Liver resection, Kyrgyzstan epidemiology, Treatment

PE-365

Developing a Preoperative Serum Metabolome-Based Recurrence-Predicting Nomogram for Patients with Resected Pancreatic Ductal Adenocarcinoma

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Aims: The metabolome represents the final stage in the "omics" cascade and is may be the closest phenotype to the biological behavior of cancer. Thus, we investigated potential clinical applications of preoperative serum metabolomes in predicting recurrence in patients with resected pancreatic cancer.

Methods: From November 2012 to June 2014, patients who underwent potentially curative pancreatectomy for pancreatic ductal adenocarcinoma were examined. We evaluated the clinical application of preoperative serum metabolomes in predicting cancer recurrence and the relationships between metabolomes and tumor markers to propose a nomogram.

Results: Among 57 patients, 32 were men; Forty-two patients had pancreatic head cancers. The 57 patients could be clearly categorized into two main clusters using 157 preoperative serum metabolomes. Patients within cluster 2 showed early tumor recurrence compared with those within cluster 1 (P = 0.034). A nomogram was developed for predicting the probability of early disease-free survival in patients with resected pancreatic cancer. Preoperative cancer antigen (CA) 19-9 levels and serum metabolomes PC.aa.C38_4, PC.ae.C42_5, and PC.ae.C38_6 were the most powerful preoperative clinical variables to predict 6-month or 1-year cancer recurrence-free survival after radical pancreatectomy, with Harrell's concordance index of 0.823 (95% CI: 0.750–0.891) and integrated area under the curve of 0.816 (95% CI: 0.736–0.893).

Conclusions: Patients with resected pancreatic cancer could be categorized according to their different metabolomes to predict early cancer recurrence. Preoperative detectable parameters, serum CA 19-9, PC.aa.C38_4, PC.ae.C42_5, and PC.ae.C38_6 were the most powerful predicting factors for early recurrence of pancreatic cancer.

PE-366

Laparoscopic Repeat Liver Resection: Short-Term Outcomes

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Aims: Laparoscopic liver resection (LLR) is now accepted as a primary tool of surgery for many liver tumors including hepatocellular carcinoma (HCC) and metastatic liver tumors. Repeat LLR (R-LLR), however, is performed far less frequently. So the authors conducted this study to evaluate the short-term outcome of R-LLR.

Methods: We reviewed a prospectively collected database of 100 patients who underwent laparoscopic liver resections (LLR) from Aug 2008 to Oct 2018. Data of 10 patients undergoing R-LLR were analyzed and compared to 1) the primary LLR group (P-LLR, n = 90) and 2) repeat open liver resection group (R-OLR, n = 20), that was performed during the same period for almost the same indications.

Results: There was no perioperative mortality in any of these 120 patients. 10 R-LLR's were performed for HCC (5), colorectal liver metastasis (3), prostatic cancer liver metastasis (1) and liver cyst (1). Open conversion rates were 20% for R-LLR and 3% for P-LLR (P = 0.077). Between the repeat and primary LLS groups, there was no significant difference in operative time, intraoperative bleeding amount, intraoperative transfusion rate, length of stay (LoS) and postoperative complication rates. When compared R-LLS group to R-OLR group, operative time and length of stay were different significantly, favoring laparoscopic approach for repeat liver resection.

Conclusions: Repeat liver resection can be done by laparoscopic approach safely and with shorter operative time and length of stay than by open approach in selected patients. More experiences are needed to define the role of repeat-LLR for recurrent liver tumors.

PE-367

Is Laparoscopic Liver Resection for Hepatocellular Carcinoma Safe for Obese Patients?

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Aims: Obesity is generally reported to increase the risk of surgical complications. Data on the perioperative outcomes of laparoscopic liver resection (LLR) in patients with obesity are scarce. The purpose of this study were to analyze the outcomes of obese patients undergoing LLR for HCC and to compare these to the outcomes of obese patients undergoing open liver resection (OLR).

Methods: We reviewed medical records of patients with HCC who underwent liver resection between July 2007 and April 2016 at our center. LLR was performed in 100 obese patients, while OLR was performed in 807 obese patients. For group comparisons, 1:2 PSM was used with covariates of baseline characteristics, including tumor characteristics and surgical liver resection procedures.

Results: After PSM, there were 69 and 138 patients in the LLR and OLR groups; The both group included 46 (66.7%) and 94

(68.1%) patients with liver cirrhosis, and 48 (69.6%) and 97 (70.3%) patients underwent anatomical resection, respectively. For perioperative outcomes, the LLR obese group had significantly shorter postoperative hospital stays (mean 8.64 days in LLR vs 14.18 days in OLR, $P < 0.001$) and lower maximum pain score (mean 4.6 in LLR vs 6.9 in OLR, $P < 0.001$) than the OLR obese group. Moreover, there were no significant differences in morbidity between the LLR obese group and the OLR obese group (13.04% in LLR vs 14.49% in OLR $P = 0.773$).
Conclusions: Our experience suggests that obesity should not be seen as a contraindication for LLR, which is a safe and feasible option for obese patients, ever for HCC treatment.

PE-368

Using of Wearable Recording Technology for Surgical Training Video in Living Donor Liver Transplantation

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Aims: As surgical video recording technology has developed, trainee education using educational video has been made.In case of laparotomy, video recording system using a surgical video crane has been introduced and many surgeons present own video in congress or society meetings. However, the view in the surgical field is different from that of the surgical video.In addition, when the first assistant or operator concentrates the focus on the field, it is difficult to actually capture what their hands are doing. In other words, recorded video has a limitation in terms of education because it does not carry all the role of the participant.
Methods: A head mount was used to fix the camera on the operating surgeon's head. The recorded video was subsequently edited and used as a teaching tool. The procedure recorded were recipient hepatectomy, hepatic vein anastomosis, portal vein anastomosis, hepatic artery anastomosis, bile duct anastomosis. Each video clip were edited for trainee education including indicator, subtitles and narration.
Results: The recorded video clips were high quality, which allowed for zooming and visualization of the surgical anatomy clearly. The camera can be mounted on the surgeon's head, so we could get a view of surgeons or 1st assistant. The trainees were able to perform image training through video before entering the surgery and showed a little more adaptation to surgery
Conclusions: Head-mounted action camera video recording system is a good model for making high quality, educational video module, and can be a useful teaching tool in living donor liver transplantation surgery.

PE-369

Robotic Simultaneous Resection for Colorectal Liver Metastasis: Feasibility for All Types of Liver Resection

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Aims: Laparoscopic approach is increasingly utilized in simultaneous colorectal and liver resection (SCLR) for colorectal cancer with liver metastasis. However, this approach is technically challenging, hence not widely adopted. The robotic surgical system could potentially overcome this problem. Thus, we aim to describe the feasibility and outcomes of robotic SCLR for colorectal carcinoma with liver metastasis using the da Vinci Surgical System.
Methods: The medical records of 12 patients who underwent robotic SCLR for colorectal cancer with liver metastasis between January 2010 and September 2018 were prospectively reviewed.
Results: : Liver resections included 2 right hepatectomy, 1 left hepatectomy, 1 left lateral sectionectomy, one segmentectomy of S3 and wedge resection (segment 7), 1 caudate lobectomy, 1 associated liver partition and portal vein ligation for staged hepatectomy, and 5 wedge resections (segments 4,5,6,7, and 8). Colorectal procedures included 7 Low anterior resection, 2 anterior resection, 2 right hemicolectomy, and 1 left hemicolectomy. The mean operative time was 449+205.1 minutes, blood loss of 274.3+210.0 ml, and length of hospital stay was 12+6.6 days. No conversion to laparotomy. Liver resection-related complications included two liver abscesses (Clavien-Dindo classification, one grade II and one grade III) and one ascites (grade I), whereas colorectal resection-related complications included one anastomosis leak (grade III) and one superficial wound infections (grade II). There was no reported 30 days mortality. Overall survival and disease-free survival was 75.2 and 47.1 months, respectively.
Conclusions: Robotic SCLR for colorectal neoplasm with liver metastasis can be performed safely even in cases requiring major liver resections.

PE-370

Parenchymal Preserving Hepatectomy in Perihilar Cholangiocarcinoma

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Aims: Despite the surgical advancement of perihilar cholangiocarcinoma (PHCC), mortality is still high owing to postoperative liver failure (POLF). This study aimed to evaluate the surgical outcome of parenchymal preserving hepatectomy (PPH) in treating patients with insufficient future remnant liver volume after hepatectomy.
Methods: Between January 2000 and December 2018, 326

patients underwent surgical resection of PHCC at Severance Hospital. Of these patients, 89 (27.3%) were predicted to have an average future remnant liver volume is less than 25~30% after hepatectomy in preoperative image. These patients were divided into two groups by different surgical strategy: one group underwent portal vein embolization (PVE) before major hepatectomy [PVE group, n = 69], and another group underwent one stage PPH without PVE in consideration of the risk of postoperative morbidity and mortality [PPH group, n = 20]. Perioperative outcome and long-term survival were compared between two groups.
Results: PVE were performed in case of advanced hilar bile duct involvement than PPH group (P = 0.002) Time to surgery and intraoperative blood loss was significantly lower in PPH group (P = 0.015 and P = 0.027, respectively) No meaningful POLF had developed in PPH group. Conversely, hospital death from POLF occurred 8 patients (11.5%) in PVE group. (P < 0.001) Disease free survival and overall survival rates were not statistically different between two groups (P = 0.882 and P = 0.191, respectively)
Conclusions: PPH procedures showed acceptable curability, morbidity and mortality rates. PPH could be an alternative option in selected patients with insufficient liver volume as well as high risk of postoperative morbidity and mortality for treating PHCC. Further following study should be required.

PE-371

Analysis of Proximal Ductal Resection Margin in Patients with Hilar Cholangiocarcinoma

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Aims: Ductal resection margin status for hilar cholangiocarcinoma is an established prognostic indicator. survival following resection in patients with positive ductal margins has generally been deemed unsatisfactory.
Methods: All consecutive patients who underwent curative intent resection for a histologically confirmed perihilar cholangiocarcinoma at our institution between 2005 and 2015 were identified from a prospectively collected database. Proximal margin was divided into negative (R0, n = 226), positive with BilIN3 (R1 Bil3, n = 10), positive with invasive cancer (R1, n = 53). Frozen biopsy examination of proximal bile duct margin revealed BilIN3 in 7 patients. Additional resection was performed in 4 of 7 patients. After additional resection margin negative was achieved in only 3patients
Results: In terms of survival, the difference between R1 and R0 was shown (median survival time[MST] 27months vs 39 months, P = 0.022). However, R1 Bil3 was better than R1 in terms of survival and recurrence., but showed no clinical significance (MST 65months vs 27months, P = 0.22, median time to recurrence 47 months vs 17months, P = 0.11). There was no statistical significance between R1 Bil3 and the secondary R0 after additional resection and the primary R0, there was no noticeable trend in survival, recurrence and recurrence types.
Conclusions: Although the cases were small and did not show any clinical significance, our study found that proximal duct margin with BilIN3 did not show adverse effect on survival and recurrence. So It is assumed that further additional resection of positive margin with BilIN3 does not yield much benefit to the survival or recurrence.

PE-372

Radical Excision for Huge Hepatic Cystic Neoplasm by Totally Laparoscopic Liver Resection: A Case Report

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Aims: Laparoscopic liver resection (LLR) has become increasingly popular and reliable in the field of hepatobiliary surgery. However, the procedure has demand the technique and experience of the surgeon on both laparoscopic and open liver surgery. Because of the lack of space and difficulty for handling of liver, LLR is hard to apply for huge hepatic mass. I introduce the case of LLR for huge hepatic cystic neoplasm in this case.
Methods: A 25-year-old male who had developed right upper abdominal pain with 2 weeks had revealed 15*8 cm sized huge and multiple cystic neoplasms with multiple internal septation focal enhancing portion located in segment 4, 5 and 6 by imaging studies. His body mass index (BMI) revealed 37.4 kg/m^2, but he has no comorbidity except obesity and no abnormality on laboratory findings.
Results: He underwent totally laparoscopic S4b/S5/S6 trisegmentectomy with cholecystectomy. Operation time was 445 minutes and intraoperative estimated blood loss was 970mL. The retrieved specimen through suprapubic incision was measured by 18.0*17.0*9.5 cm and 880 gm. Final pathology revealed pleomorphic sarcoma, most-likely leiomyosarcoma which was 16.0*11.0*9.0 cm with FNCLCC grade 3 and no involvement for resection margin. He discharged at postoperative 9th day without problem.
Conclusions: Primary hepatic leiomyosarcoma is very rare soft-tissue tumor. Even though rarely been reported in this tumor, hepatic resection is associated with encouraging rates of overall and disease-free survival. When huge hepatic cystic neoplasm is hard to distinguish between benign and malignancy before operation, LLR can be a choice for diagnosis and treatment like this case.

PE-373

Optimum Timing of Emergency Cholecystectomy for Acute Cholecystitis

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Aims: Cholecystectomy on index admission for acute cholecystitis is associated with improved patient outcomes. The timing of intervention is mainly driven by service provision. This population-based cohort study aimed to evaluate timing of emergency cholecystectomy in Almaty.
Methods: Data from all consecutive patients undergoing surgery for acute cholecystitis on index admission in Almaty from 2010 to 2016 were captured from the Hospital Episodes Statistics database. Data were analysed based on whether patients underwent surgery 0-3 days, 4-7 days or ≥8 days from admission. Outcome measures were rate of post-operative biliary complications, conversion to open and length of stay.
Results: Two thousand three hundred and seventy six patients underwent emergency cholecystectomy. 64.6% of patients underwent surgery between days 0 and 3 of admission, 24.3% between days 4-7 and 11.0% had surgery after day 8. Patients undergoing early surgery had significantly reduced rates of intra-operative laparoscopic conversion to open (0-3 days: 3.6%; 4-7 days: 4.0%; ≥8 days 4.7%, p=0.001), post-operative Endoscopic Retrograde Cholangio-Pancreatography (0-3 days: 1.1%; 4-7 days: 1.5%; ≥8 days 1.9%, p<0.001) and bile duct injury (0-3 days: 0.6%; 4-7 days: 1.0%; ≥8 days 1.8%, p<0.001). Early cholecystectomy was also associated with a shorter post-operative length of stay (LOS) [0-3 days group: median post-operative LOS 3 days (IQR: 1-6); 4-7 days group: 3 days (IQR 2-6); ≥8 days group: 4 days (IQR 2-9) (p<0.001)]. High-volume centres undertook a significantly greater proportion of cholecystectomies within 3 days of presentation (high-volume: 67.3%; medium-volume: 64.8%; low-volume: 61.2%). In multivariate analysis greater time to surgery was independently associated with increased risk of post-operative Endoscopic Retrograde Cholangio-Pancreatography and bile duct injury.
Conclusions: Early cholecystectomy within 3 days of admission reduces intra-operative conversion, post-operative biliary complications and length of stay. Centres undertaking the greatest numbers of emergency cholecystectomies perform a larger proportion within 3 days of admission.
Keywords: Cholecystitis, Acute, Emergency cholecystectomy

PE-374

The Immediate Results of Surgical Treatment of Liver Hemangiomas

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Aims: The aim of the work is to evaluate the results of surgical treatment of liver hemangiomas.
Methods: The work is based on the analysis of liver resection results of 19 patients, 13 women (68.4%) and 6 men (31.6%), the ratio is 2: 1, the age ranged from 16 to 69 years. Disease duration was from 1 month to 15 years, it's the period when they had signs of the disease, which consisted of the appearance of weakness, heaviness and dull pain in the right hypochondrium and epigastric region. Ultrasound examinations (19 patients) and CT scans (19 patients) of the liver were performed in all patients and several patients with giant hemangiomas of the liver underwent a MSCT (3 patients) to detect compression of the vessels and bile ducts of the liver.
Results: As a result of the study, the right lobe of the liver was affected in 11 patients (57.8%), the left lobe was affected in 8 patients (42.1%), 3 or more affected segments were detected in 10 (52.6%) patients, the lesion 2 segments in 7 (36.8%) patients and 1 segment damage in 2 (10.5%) patients. Of these, 4 (21%) patients underwent right-sided hemihepatectomy, left-side hemihepatectomy was performed in 1 (5.2%) patient, 15 (78.9%) patients underwent atypical liver resection, including a lobectomy was performed in one patient and 2 (10.5%) patients had an exploratory laparotomy. The maximum blood loss was about 1.5 liters; the minimum blood loss was 200 ml. Nine patients underwent simultaneous operations. As a result of the histological conclusion, cavernous hemangioma was confirmed in 15 (78.9%) patients, in 1 (5.2%) of the patient - the capillary liver hemangioma, in 1 (5.2%) of the patient the data for large-site cirrhosis of the liver, in 1 (5.2%) of the patient data for hepatocellular adenoma, in 1 (5.2%)of the patient chronic granulomatous inflammation. 6 patients had comorbidities such as cholelithiasis, hypertension and diabetes mellitus.
Conclusions: Thus, liver resection is an effective and affordable method for the treatment of liver hemangiomas. Giant hemangiomas, fast-growing hemangiomas and hemangiomas with the threat of rupture are absolute indications for surgical treatment. Ultrasound, CT and MSCT of the liver in the preoperative period allows to determine the volume of the intended operation.
Keywords: Results of surgical treatment, Liver hemangiomas, Liver resections, CT

PE-375

Surgical Treatment of the Liver Alveococcosis, Complicated by the Mechanical Jaundice

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Aims: to evaluate the results of surgical treatment of liver alveococcosis complicated by obstructive jaundice.
Methods: 69 patients' case histories undergoing inpatient treatment were analyzed at the Department of Surgical Gastroenterology and Endocrinology of the National Hospital under the Ministry of Health of the Kyrgyz Republic. During the period 2009 to 2019, 440 patients received surgical treatment for alveococcosis of the liver, 69 of them (15.68%) were patients with complicated mechanical jaundice form of alveococcosis, 38 of them (55.07%) were women and 31 (44.93%) were

men. The average age of patients was 37.3 ± 3 years. All patients undergoing treatment were given a blood test for liver tests, the results of which characterized the pattern of obstructive jaundice

Results: To improve the general condition of patients, percutaneous-transhepatic drainage of the bile ducts for the purpose of decompression was performed, to resolve questions about the volume of the operation and also as a stage of preoperative preparation. After 2-3 weeks, in 90% of patients laboratory values reached the normal range, which allows for radical surgery. The choice of tactics and the volume of the operation depends on the size, localization of alveolar nodes. 69 patients with alveococcosis of the liver complicated by obstructive jaundice, 6 of them (8.7%) underwent liver resections, with hepaticocholedochitis resection with hepaticojejunostomy. 6 (8.7%) extensive liver resections were performed. 2 (2, 9%) atypical resections of the liver were performed., 2 (2.9%) related liver transplantation (India)., Resection using transplant technologies: 4 (5.8%) ("invivo - insitu")., 2 (2, 9%) ("exvivo – exsitu").

Conclusions: The best option for surgical treatment of alveococcosis of the liver complicated by obstructive jaundice is decompression of the bile ducts, liver resection performed within healthy tissues. In cases of impossibility of carrying out a radical operation, it is necessary to carry out biliary tract decompression in patients with obstructive jaundice, which will improve the quality of life of patients during the period of preparation for a liver transplantation.

Keywords: Liver alveococcosis, Mechanical jaundice, ALT, AST

PE-376

X-Ray Endobiliary Methods in the Treatment of Patients with Alveococcus of the Liver, Complicated by Mechanical Jaundice

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Aims: To improve the results of treatment of patients with obstructive jaundice of alveococcal etiology by optimizing the tactics of surgical treatment using percutaneous, transhepatic interventions. To estimate the number of patients who need percutaneous-transhepatic drainage for obstructive jaundice of alveococcal genesis and its effectiveness in relieving obstructive jaundice.

Methods: From the period from April 2009 to April 2017, 31 (11%) were admitted with obstructive jaundice.

Results: In 21 patients, the level of bilirubin was more than 124 μmol/l, in this regardthey were held RHHE and percutaneous-transhepatic drainage. Of these, 12 women (57.1%), men 9 (42.9%) aged 16 to 62 years old, the average age of patients was 33.2 ± 9 years. The average level of bilirubin at admission was 252.4 ± 35 μmol max-543, min- 124. In the postoperative period, the improvement in the general condition was observed already for 2 days, and the average level of bilirubin in the postoperative period was 149 ± 24 mmol/l with a tendency to decrease with further dynamic, and in the subsequent and dispensary observation.

Conclusions: Percutaneous transhepatic cholangiostomy is one of the widely spread, widely used and effective methods of surgical treatment of patients with mechanical jaundice of alveococcal genesis, which allows to achieve adequate drainage of the bile ducts. At the moment, the operation is one of the stages of treatment of patients with alveococcosis of the liver. In the first case, this is preparation before a radical liver resection, in the second case, it is a palliative operation in inoperable patients who are prescribedto have a liver transplant.

Keywords: X-ray, Endobiliary methods, Liver alveococcus, Mechanical jaundice

PE-377

Advantages of Kasai Procedure through Minimally Invasive Approach in Children with Biliary Atresia

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Aims: To compare early and long-term results of different surgical interventions in children with biliary atresia.

Methods: Retrospective analysis included medical records of children with biliary atresia who were treated at the Filatov Munitsipal Children's Hospital and National Medical Research Center for Obstetrics, Gynecology and Perinatology from 2000 to 2018. There were 91 patients. All patients were divided into three groups. Group 1 - conventional Kasai procedure (n = 24), group 2 - laparoscopic Kasai surgery (n = 45), group 3 - Kasai procedure through minimally invasive approach (n = 22). Groups were comparable.

Results: Duration of Kasai procedure through minimally invasive approach was 69±12,97 min that was significantly less than in groups 1 and 2 (p1,3=0,006085; p2,3=0,000024). ICU-stay was minimal in group 3 (1.27±0.55 days, p1,3<0,05; p2,3<0,05). Abdominal drainage time was maximal in group 2 (11.28±6.37 days) and minimal in group 3 (5.86±2.39 days, p2,3=0.0002). Early and 2-year postoperative surgical efficiency was similar in all groups. There were no surgical complications in group 3. In group 2 one child had gastrointestinal bleeding followed by successful medication. There were 3 surgical complications in group 3: adhesive intestinal obstruction, small and large intestine perforation and 2 cases of gastrointestinal bleeding. There was one lethal outcome in the first group. Overall annual survival in children with native liver was 81.8%, 2-year – 51.7%.

Conclusions: Kasai procedure through minimally invasive approach is justified and rational method with certain benefits of

open and laparoscopic interventions and can be considered as a method of choice in treatment of children with biliary atresia.
Keywords: Kasai operation, Biliary atresia, Laparoscopy, Minimally invasive approach

PE-378

Transplantation Technologies in Surgical Treatment of Advanced Liver Alveococcosis

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Aims: Results analysis of surgical treatment of advanced liver alveococcosis with using transplantation technologies
Methods: From 2008 to 2019 in «Volga district medical center» were operated 58 patients with liver alveococcosis. Mean age of patients being 38.7 years. Male/female ratio is 14/41. The complications of the underlying disease were in 47% (45% – obstructive jaundice, portal hypertension – 25,8%). 53% patients were previously non-radical operated. In common group 62% of patients (n = 36) had advanced alveococcosis with involvement's of afferent and efferent vascular, biliary. Extrahepatic alveococcosis foci were revealed in 4% patients (lungs, brain). The size of a parasitic node in the liver varied from 9.3 to 21.7 cm.
Results: 58 patients underwent radical surgeries: 52 had R0 resections, 5 – orthotopic liver transplantations + 1 living donor transplantation. In group of resections 62% were extended resections (≥4 Sg), vascular reconstructions were in 47% cases (IVC – 28 cases, PV – 24 cases). In 34 cases was performed resection of extrahepatic bile ducts with subsequent reconstruction, resection of adjacent organs such as the diaphragm, lung, right adrenal gland, duodenum, stomach, and large intestine were performed in 33%. In 5 cases were "ex vivo" resection followed by autotransplantation, in 3 cases with a reverse autotransplantation of the left lateral sector. The incidence of PHLF degree A and B (ISGLS) did not exceed 10%. Complications (Clavien-Dindo) in 32 cases: grade II-8, IIIb-15, IVb -2, V-7. Bileleakage (ISGLS): class B -7, class C-13. All patients treated with obligate adjuvant antiparasitic therapy.
Conclusions: 1. Liver resections in patients with advanced liver alveococcosis are the method of choice for treatment. 2. "ex situ ex vivo" liver resection can be regarded as an alternative to liver transplantation, which allows to avoid lifelong immunosuppression and significantly improves the quality of life.
Keywords: Liver alveococcosis, Liver transplantation, Extracorporal "ex vivo" resection, Hepatectomy

PE-379

Surgical Treatment of Liver Alveococcosis

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Aims: generalized alveolar disease - alveolar or multi-helminthiasis, caused by larvae of Echinococcus multilocularis, is characterized by the formation of parasitic nodules in the liver.
Methods: in total, 54 patients with liver alveococcosis were treated in the period from 2008 to 2018 under the conditions of Aktobe medical center and the regional medical center of Kyzylorda, including 34 men and 20 women. The disease was found mainly in young and middle-aged people (mean age was 35±3,6 years). The right proportion of the liver was affected in 32 patients (60.0%), the left – in 13 patients (25.5%), the defeat of both shares was noted in 9 (14.5%) patients.
Results: a total of 58 surgical interventions were performed, with one patient having 2 for one hospitalization, the first - lumping of the tumor, and the second – liver transplantation. Right-sided hemihepatectomy-12, left-sided hemagepatectomy-8, trisegmentectomy-6, bisegmentectomy-6, segmentectomy-2, palliative surgery-22, liver transplantation-2.
Conclusions: liver Alveococcosis is a relatively rare but insidious disease with severe complications, especially in epidemic foci, and requires unification of diagnostic and therapeutic measures. Radical method of treatment for alveococcosis is liver resection of different volumes. Surgical carbon dioxide laser providing reliable hemostasis has shown high efficiency in performing surgical intervention, which reduces the risk of parenchymal bleeding in the postoperative period. With alveococcosis, when there is a defeat of both liver lobes, or parasitic node is localized in the liver, or there is a germination of the parasite of the inferior Vena cava, liver transplantation is possible.
Keywords: Surgical, Treatment, Liver, Alveococcosis

PE-380

The Use of Laparoscopic Echinococcectomy in the Surgical Treatment of Echinococcosis of the Liver

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Aims: Treatment of parasitic lesions of the liver remains one of the most pressing problems of surgical hepatology. The only effective treatment for liver echinococcosis is operative. New perspectives in the treatment of liver echinococcosis opens up the use of video endoscopic surgical interventions - laparoscopic echinococcectomy.
Methods: In the surgical department of the Regional Medical Center. Kyzylorda in the period from 2013-2018, performed 33 laparoscopic interventions in patients with liver echinococcosis. Among them were 19 men and 13 women aged from 15 to

58 years. The equipment of the company and the tools of the firm "Karl Storz" were used. Operations were performed under endotracheal anesthesia. Used 3 trocars. The patient was transferred to the opposite position of Tredenburg. After that turunds were injected into the abdominal cavity moistened with a solution of povidone, which was used to cover the area around the cyst. The next stage was puncture of the cyst with a thick needle with complete suction of the cyst contents with a vacuum suction. Then, through the same needle (without removing it from the cyst cavity), a 1% povidone solution was injected into the residual cavity. After exposure at 5 minutes, the cyst contents were again fully aspirated. The treatment was repeated twice. Then the cyst wall in its most thinned place was opened with electrocoagulation scissors. Excess fibrous capsules with thinned hepatic parenchyma were excised. Shells parasites were removed from the cavity of the cyst using an endocontainer. The walls of the fibrous capsule were treated with povidone solution. The drainage of the residual cavity was performed by specialized silicone drains. All operations were performed without a transition to laparotomy. Drainage from the residual cavity was removed for 3-4 days after the operation after the mandatory ultrasonic testing.

Results: Laparoscopic removal of echinococcal liver cysts was performed in all 33 patients. The average duration of the operation was 43.5 ± 3.4 minutes (from 30 to 55 minutes). In no case did we switch to laparotomy. The average length of stay in the hospital ranged from 5 to 8 days. Mortality was zero.

Conclusions: Laparoscopic echinococcectomy can be successfully used in the treatment of liver echinococcosis in patients with superficial echinococcal cysts. The absence of laparotomic incision significantly reduces the time of rehabilitation of patients after surgical treatment.

Keywords: Laparoscopic, Echinococcectomy, Liver

PE-381

Surgical Management of Patients with Mirizzi Syndrom

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Aims: To assess an effectiveness of complex preoperative diagnosis, conservative treatment, minimally invasive biliary decompression for Mirizzi syndrome and to analyze surgical outcomes depending on the effectiveness of minimally invasive biliary decompression.

Methods: There were 46 patients with Mirizzi syndrome aged 32-82 years (mean age -64 years). The diagnosis was established on the basis of complaints, objective data, laboratory survey, abdominal X-ray, ultrasound (US), endoscopic gastroduodenoscopy (EGDS), computed tomography (CT) and magnetic resonance imaging (MRI). Extrahepatic bile duct visualization in case of suspected biliodigestive fistula was achieved by using of percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography, cholecystocholangiography, intraoperative cholangiography.

Results: The analysis of the diagnosis and treatment of patients with Mirizzi syndrome and mechanical jaundice with and without symptoms of cholangitis was carried out. It should be noted that percutaneous transhepatic cholangiography and cholecystocholangiography with antegrade contrasting were able to confirm Mirizzi syndrome type 1 without complications. Retrograde cholangiopancreatography in patients with Mirizzi syndrome type 2 reduced the diagnostic value of contrast-enhancement with complications in every fifth patient. Percutaneous drainage for Mirizzi syndrome type 1 was effective in all patients. There was low effectiveness of medication for Mirizzi syndrome. Medication combined with antegrade biliary decompression was 7 times more effective than retrograde decompression. All patients underwent surgery.

Conclusions: Mortality depended on surgical emergency and effectiveness of biliary decompression. So, emergency interventions were followed by mortality rate near 60% while there were no deaths after elective procedures. Overall mortality was 11.9%.

Keywords: Mirizzi syndrome, Common bile duct

PE-382

Management of Carcinoma Gallbladder In Patients with Portal Hypertension

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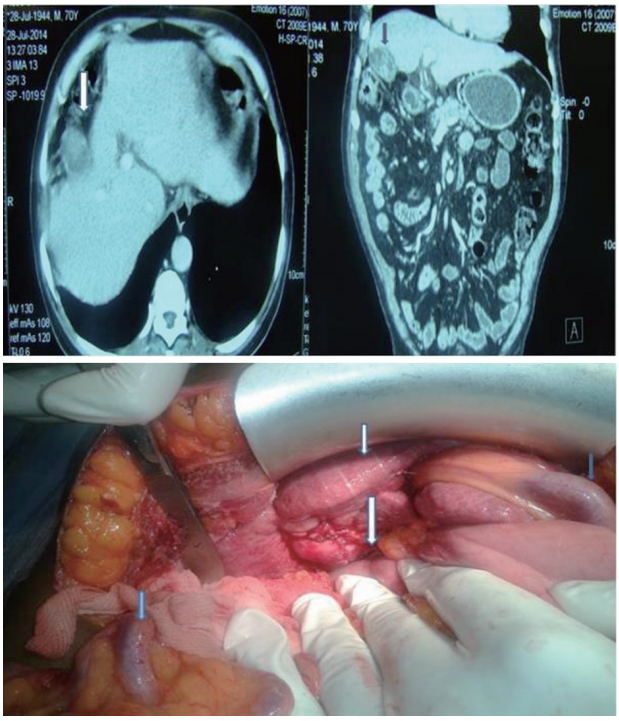
Aims: Gall bladder cancer (GBC) is one of the most common malignancy in our part of world with a poor prognosis. There is no available literature on the management of patients of carcinoma gall bladder in the backdrop of portal hypertension. This study aimed to analyze various issues faced during the surgical management of such patients and its impact on survival of such patients

Methods: 950 patients of carcinoma gall bladder were evaluated retrospectively from a prospectively maintained data base between January 2004 to March 2019 at four academic institution. During this period 404 radical cholecystectomy and 148 shunt surgery for portal hypertension were performed. Eleven patients with perioperative evidence of portal hypertension were reviewed.

Results: Of the Eleven patients, seven patients underwent surgical resection. Out of eleven, seven were male and four were

female. The median age at presentation was 50 years (range 35 to 70 years). In the non resected group one patient underwent trial dissection but surgery had to be abandoned in view of advanced carcinoma gall bladder. Another patient underwent segment III bypass in view of cirrhosis with locally advanced tumour. Two patient were not considered for surgical management due to patient's advanced Child B status.Seven patients underwent liver resection with various degree of lymphadenectomy depending upon the presence of collaterals. There was no early postoperative mortality in any of the resected patients. Median postoperative stay was five days (range 4-8 days). Of all the patients who underwent resection, one patient died after forty months, secondary to alcohol related (nonabstinent) liver failure. Two patients died at 43 and 49 months respectively due to tumour recurrance. Four patients are surviving at the time of analysis with median survival of 40 months (range 7-148 months).



Conclusions: Survival in patients who underwent resection was not found to be inferior to the resected carcinoma gall bladder patients without portal hypertension. None of the non resected patients had long survival. Surgery should be offered to the patients of resectable GBC with Child A or early Child B liver disease as these patients are not good candidates to receive chemotherapy as well. Lymphadenectomy may need to be modified in the presence of extensive collaterals. Assessment of ascitis can be tricky. Placement of umblical port for staging laparoscopy can lead to injury to peri umblical collaterals. Poor nutritional status secondary to liver cirrhosis increases rate of post-operative complications. Impaired synthesis of clotting factors, decreased vitamin K stores by diseased liver and decreased platelets may lead to coagulopathy and bleeding.

Keywords: Gall bladder carcinoma, Portal hypertension

PE-383

Liver Transplantation Outcomes in UMC

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Aims: Liver transplantation is the only life-saving intervention for patients with end stage liver disease. LDLT donors are typically healthy adults who do not derive any medical benefit from the procedure for themselves. Donor death is the most serious complication after LDLT, with estimated mortality at 0.28 to 1.0 percent, however, the exact risk cannot be precisely quantified due to the lack of a centralized database measuring donor outcomes.

Methods: We retrospectively reviewed the medical records of 604 LDLT recipients who underwent the procedure using a right liver graft between May 1999 and September 2012 in the Department of Surgery. Donor age, sex, and the degree of hepatosteatosis were compared between the groups. Recipient age, sex, body mass index (BMI), and transplantation indications were also compared between the two groups. We measured the recipients' Child-Turcotte-Pugh (CTP) and Model for End-stage Liver disease (MELD) scores in both groups to compare the preoperative disease severity. Although the general donor age recommendation in our institution is 16-55 years of age, the donors in this study were 16-67 years old.

Results: The anatomical structure of the vasculature and biliary tree and liver consistency were evaluated using abdominal CT, ultrasonography, and magnetic resonance cholangiopancreatography (MRCP). A frozen section liver biopsy to evaluate the degree of hepatosteatosis was performed in all of the donors during the operation. All of the hepatic grafts were perfused and preserved with iced HTK solution.

Conclusions: LDLT using elderly donors could induce more serious complications and higher mortality rates than those at using younger donors. As such, careful donor selection is needed, especially with regard to assessing the condition of potential elderly donor livers. Furthermore, a large-volume and multicenter study of complications and outcomes of LDLT using elderly donor liver is required.

Keywords: Liver, Transplantation, Donor, Recipient

PE-384

Finger Fracture Technique with Glissonian Pedical Approach for Liver Resection Is Comparable to All Other Techniques for Liver Resection

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Aims: In modern world there are many devices available for liver transection with clamp crushing method is still god standard. Finger fracture technique is rarely used recently. We use finger

fracture technique with glssonian pedical technique to reduce operative time and anesthetic related complications.
Methods: We performed liver resection using glissonian pedical approach and parenchymal transection using finger fracture technique. Average operatime time, blood loss, bile leaks and any other complication noted and compared with standard literature. Major liver resection defined as resec- tion of two adjacent segments.
Results: Sixteen patients were under went liver resection with above techniques two patients under gone left trisegmen- tectomy for hilar cholangio carcinoma, two patient under went right posterior sectorectomy for hepatocellular carci- noma, one patient left hepatectomy for hepatocellular car- cinoma, two patients underwent right hepatectomy for hepatocellular carcinoma,one patient segment 8 resection for liver metastasis, one patient left lateral segment resec- tion for liver trauma and four patient underwent segment 4b5 resection for ca GB. Two patients underwent non anatomic resection for hcc in case of 2 or 3 lesions. Mean operative duration was 3 hrs compared to 4-5 hours by literature in other techniques. Mean blood loss was 270 ml. two patient developed minor bile leaks -which settled down with conservative treatment at 2 weeks. One patient expired due to post operative MI diagnosed by echo,ecg and cardiac markers.
Conclusions: Fingure fracture technique with glissonian pedical approach is rapid method for liver resection with comparable outcomes to all other techniques.

PE-385

Microwave Assisted Liver Resection: Clinical Feasibility Study and Preliminary Results

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Aims: The main goal of liver resection for malignant tumors is nowadays represented by properly parenchymal transection and careful control of hemostasis. Applying the concept of precoagulation of liver transection line we developed a new technique that provides the pre coagulation of the resection line using microwaves technologies. The purpose of this study is to evaluate the feasibility of this newliver performance of this procedure, the accuracy in terms of squeeze effect on veins and portal branch and in terms of reducing the intra operative blood loss.
Methods: From December 2016 to January 2018 a total of ten patients (6 men and 4 women) affected by liver metastatic disease from colon rectal cancer and primitive liver cancer were treated (five patients with metastatic colorectal cancer disease and five patient with hepatocellular carcinoma respectively.
Results: The technique used for the parenchyma transection is similar to those previously described by our group for hepatic radiofrequency assisted liver resection. There was no need for vascular occlusive clamping while during each surgical procedure the underpass of the hepatic hilum was done for safety control of any kind of hepatic bleeding.
Conclusions: In conclusion this study with a small group of patients suggest surgical advantages in terms of statement for best practice in oncologic resection of liver malignancy. It allows a complete resection obtaining a negative pathologic margin, no blood loss and need for blood transfusions factors predicting post operative morbidity and survival, and consistently reducing time of procedure and avoidance of parenchymal ischemia.

PE-386

Pure Laparoscopic Left Hepatectomy Using Arantius' Ligament Approach Combined Glissonean Pedicle Approach

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Aims: We describe a novel extra-glissonian approach combined Arantius' ligament approach for totally laparoscopic left hepatectomy. The extra-glissonian approach and Arantius' ligament approach have proven useful in open surgery for left hepatectomy. And these approachs could be even more useful in the laparoscopic context.
Methods: The study included 11 patients who underwent totally laparoscopic left hepatectomy between July 2016 and September 2017. Arantius' ligament was then identified, encircled and divided. Retracting the caudal stump of the ligament revealed a space between the left Glissonean pedicle and the liver parenchyma. The left Glissonean pedicle was encircled extrahepatically with a cotton tape and transected with an endostapler. The parenchymal dissection then proceeded to the left hepatic vein, which was finally divided. The specimen was placed in a plastic endobag, and extracted through a suprapubic incision.
Results: No postoperative mortality was encountered and no Glissonean injuries, including bleeding or biliary leakage, occurred. The mean length of surgery was 290113 min, and the mean blood loss was 350187 ml. The mean duration of hospital stay was 11.73.5 days. Pathology showed free surgical margins.
Conclusions: The Arantius' ligament approach combined Glissonean pedicle approach appears to be feasible and safe for successfully performing totally laparoscopic left hepatectomy.

PE-387

Cystobiliary Communication in Hydatid Disease: A Recalcitrant Problem

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Aims: Echinococcus granulosus has a propensity to cause hepatic infection in infected humans. Surgery still remains the main curative option for large hydatid cysts. Recognition and management of cysto-biliary communications (CBCs) are of upmost importance given the increased risk of peri-operative morbidity and mortality.

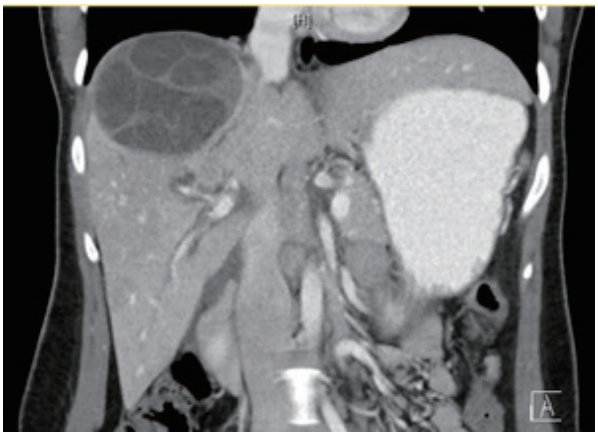

Figure 1. Multiloculated segment 8 liver cyst.

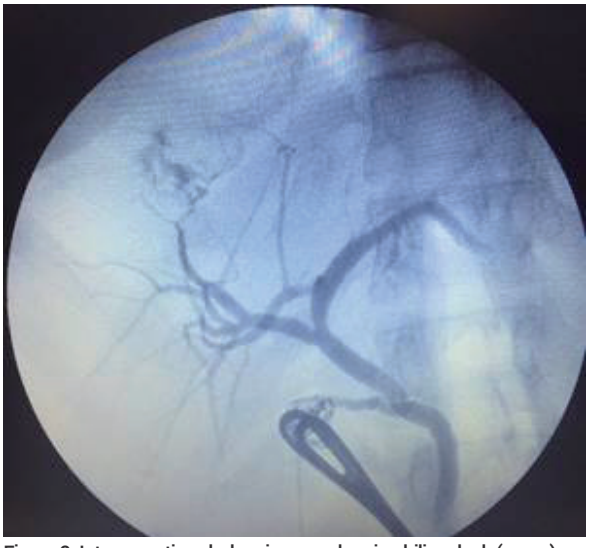

Figure 2. Intraoperative cholangiogram showing biliary leak (arrow)

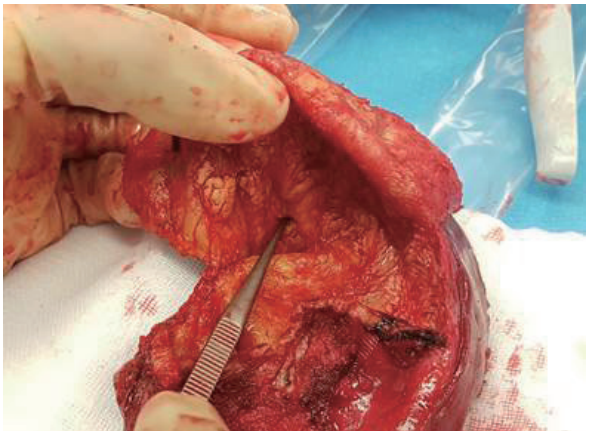

Figure 3. Cysto-biliary communication with thick walled cyst.

Methods: A 22 year-old female presented with 3 weeks history of right hypochondrial pain. On computer tomography a 10x8x7 cm multiseptated cystic lesion was noted in segment VIII (figure 1). There was adjacent periportal edema with biliary wall enhancement but no clear CBC was demonstrated on subsequent MRI. Her hydatid serology suggested active disease for which she started on a course of albendazole prior to surgery.

Results: At exploration a large hepatic cyst adherent to the diaphragm was noted. Given pre-operative radiological findings an intra-operative cholangiogram was performed via the cystic duct which showed third-order right anterior sectoral duct in communication with the cyst (figure 2). A cystotomy was made with 10mm laparoscopic port where bilious cyst contents were aspirated and lavaged with warm normal saline for 30 mins. The wall of the cyst was very thick and clear biliary communication was noted (Figure 3). A local liver resection was undertaken with Echelon (Ethicon) stapler. Part of the diaphragm was resected and primarily closed. Completion cholangiography and biliary injection with intralipid showed no biliary leak. However the patient developed a controlled bile leak post operatively. An ERCP showed a small persistent leak from the peripheral sectoral system. A stent was deployed and she was discharged home 10 days later.

Conclusions: Any indirect suggestion of a CBC on imaging (biliary tract enhancement or edema) requires intraoperative cholangiography. CBC from hydatid disease can be difficult to control with stapling devices. It may be better to use CavitronUltrasonicSurgicalAspirator and ligate the communicating duct instead.

Keywords: Hydatid cysts, Cystobiliary communication, Cholangiograms

PE-388

Early Experience of Single Port Robotic Cholecystectomy Using Da Vinci Xi System

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Aims: Multiport laparoscopic cholecystectomy (MLC) is the gold standard technique for cholecystectomy. In order to reduce postoperative pain and improve cosmetic results, the application of the single-incision laparoscopic cholecystectomy (SILC) technique was introduced, leading surgeons to face important challenges. Robotic technology has been proposed to overcome some of these limitations. The aim of this work was to study the feasibility, safety, and efficacy of single site robotic (Da vinci Xi) cholecystectomy.

Methods: All operations were performed by the two surgeons. Parameters assessed included patient history, indication for surgery, operation time, complication rate, conversion rate, robot-related issues, length of hospital stay. All patients were followed for a 6-month period postoperatively.

Results: Sixty patients (48 women, 12 men) underwent single-site robotic cholecystectomy from April 2018 to April 2019. There were no conversions to either conventional laparoscopy or laparotomy. There were no major complications such as postoperative hemorrhage, bile leakage or wound complication apart from a single case of incisional hernia. Average patient age was 42 ± 9.1 (23–65)years and average BMI was 22.8 ± 2.8(17.5–29.6) kg/m^2. The primary indication for surgery was gallstones. The mean operation time (skin-to-skin) was 69.2 ± 12.9 (43–116) min. Intraoperative blood loss was negligible. There were no collisions between the robotic arms and no other robot-related problems. Average hospital stay was 3±1.1(2-8) days.
Conclusions: Single-Site® is a new platform offering a potentially more stable and reliable environment to perform single-port cholecystectomy. Both simple and complicated cholecystectomies can be performed with safety. The technique is possible in patients with a high BMI. The induction of pneumoperitoneum using the new port and the docking process require additional training.
Keywords: Cholecystectomy, Single port, Robotic

PE-389

'Falciformoplasty' as an Alternative to Omentoplasty for Deep Hydatic Cysts

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Aims: Whilst pericystectomy or partial hepatectomy achieve the highest chance of eradicating the hepatic hydatid cyst this may not always be possible in those located deep in the liver parenchyma, especially in central segments. Cyst deroofing and omentoplasty has been a favoured approach. This case report presents a technique of using the falciform ligament as a local vascular flap to plug the deep residual cavity after deroofing a deep cyst in segment IV.
Methods: A 45-year-old female was diagnosed with an active unilocular 29x42x33mm segment IV hydatid cyst on MRI (figure 1). It was found 3 cm deep to the liver surface. After a course of albendazole she was booked for open surgical intervention.
Results: Intra operative ultrasound was used to confirm its location before a 5mm laparoscopic port was placed with its tip in the middle of it. The cavity was aspirated and no bilious content was noted. Cetrimide/chlorhexidine solution was instilled for 15 minutes. The blunt tip of the port was used to curetted the wall of the cyst and aspirated. A hepatotomy was then performed to allow better access to the cyst. A well vascularised flap of preperitoneal fat with the falciform ligament as a pedicle was used to fill the cyst cavity and sutured in place (figure 2,3). There was no acute surgical complication post operatively.
Conclusions: Omentoplasty has been described as being an effective technique for managing residual cavities. A 'falciformoplasty' may be a good option for deep central cysts or if the omentum is absent.

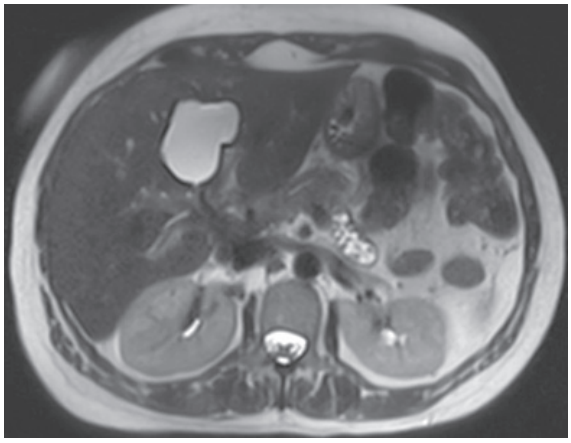

Figure 1. Axial MRI T2 phase showing unilocular cyst.

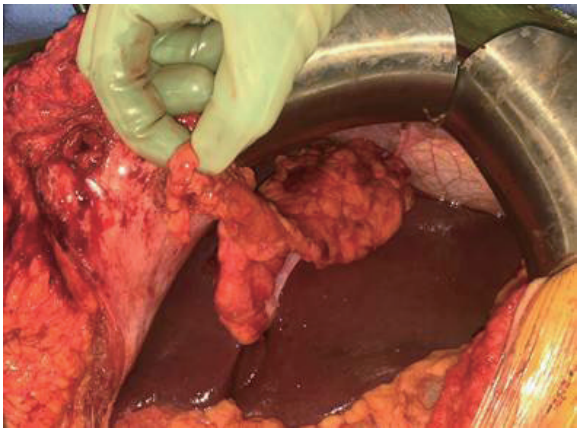

Figure 2. Preparation of falciform ligament.

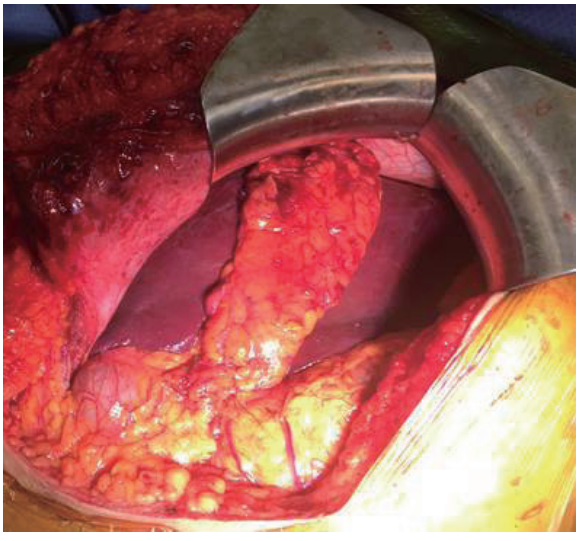

Figure 3. Post falciformoplasty.

Keywords: Falciformoplasty, Hydatid cysts

Others

PE-390

Robotic Reduced-Port Splenectomy Using Single-Site Platform: 8 Cases of Single Surgeon Experience

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Aims: The Da Vinci Robotic reduced-port splenectomy using Single-site platform permits greater freedom of movement and higher levels of accuracy than previous laparoscopic surgery through two small incisions.

Methods: We performed a retrospective review of all patients who underwent Robotic reduced-port splenectomy using Single-site platform at our institution between January,2015 and November,2018. One 3 – 4 cm long periumbilical incision and the other 8mm long incision was made at left side of abdomen. Short gastric artery was ligated with hem-o-lok clips. Splenic artery and vein were ligated individually using hem-o-lok clips. A specimen was removed through umbilical port site.

Results: 6 women and 2 man, total 8 patients with median age of 33.5 years underwent Robotic reduced-port splenectomy. The indications were; hematological disease (n = 3), splenic mass (benign n = 4, malignant n = 1). Preoperatively measured spleen size was ranged 5.5 cm to 16 cm (median = 11). There were no intraoperative complications and conversion to open surgery. The operative time ranged 74 to 216 minutes (median = 152). 2 patients experienced acute portal vein thrombosis, without elevation of serum transaminase or liver ischemia on image study. All PVT was resolved after 1 month follow up CT scan. The median follow up period was 174.5days.

Conclusions: Robotic reduced-port splenectomy using single-site platform seems to overcome certain limits of previous robotic or conventional single-site laparoscopic splenectomy and single-site only robotic splenectomy. We think 8mm additional port allows to use Endo-wrist Da Vinci instruments such as Vessel sealer which enhances dissection efficiency and- safety of procedures.

PE-391

Liver Cancer and Its Risk Factors-Related Researches in North Korea

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Aims: Liver cancer ranks 4th among top 10 cause of death in 2017 in North Korea. Its mortality rate due to liver cancer is estimated to be 17.6 per 100,000 population in 2016. This study aims to understand current status of researches in North Korea regarding liver cancer and its risk factors.

Methods: Literature review of medical journal published in North Korea was conducted. Articles in *Preventive Medicine* from 2003 to 2018 were reviewed. A total of 2545 articles were published during this period. Among them, articles related with liver cancer and major risk factors including hepatitis B infection, hepatitis C infections, alcohol consumption, aflatoxin B1, obesity, diabetes and liver flukes, and related treatment were selected and analyzed by features.

Results: Among 2,545 articles, 197 articles were associated with risk factors and related treatment of liver cancer and 22 articles were related with liver cancer. In an epidemiological study targeting patients with hepatic diseases, proportion of acute hepatitis, chronic hepatitis, and liver cirrhosis was 24%, 55%, and 21%, respectively. The ratio by virus type of hepatitis B, hepatitis C, and NBNC was 21.4:1:2.6. Chronic hepatitis infection was highest among those in 30s and 40s, while liver cirrhosis was highest among those in 40s and 50s. The ratio of men to women for chronic hepatic disease was 3:1. For liver cancer, mortality rates in some areas ranged from 1.50 ±0.23 to 2.46±0.20 per 10,000 persons. Questionnaire for selecting risk group of liver cancer in mass screen was found and detection rate was 1.4%. Survival rates of the patients with the mass size of 5.0~7.9 (cm) were 42.6% for 2 years.

Conclusions: Epidemiological features and current status of researches regarding liver cancer, its risk factors and related treatments in North Korea were analyzed through literature review of articles in medical journal published in North Korea.

Keywords: Liver Cancer, Hepatitis, North Korea, Risk Factors

PE-392

Feasibility of Continuous Venous Infusion in a Porcine Hepatectomy Model

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Aims: Subcutaneous injection of drugs has been used for continuous drug treatment in animal studies due to continuous intravenous infusion device is not stable because of the movements. We established stable injection method using continuous intravenous infusion device in a porcine.

Methods: Forty-four domestic female crossbred Yorkshire-landrace and duroc porcine (approximately 35~40kg, 2 to 3 months old) were used in this experiment from September 2017 to February 2019. A disposable infusion device using self -produced CO2 as power source (ANAPA-Chemorherapy®) was used to maintain a constant flow rate for 50 hours. Open cut down method was used for venous access. After general anesthesia, 5 cm vertical incision was made besides the thyroid cartilage.

The central venous catheter was inserted to the internal jugular vein and made a tunnel to the mandible through the subcutaneous tissue. The disposable infusion device was fixed to the harness with a porcine. Extension line of leur lock type was connected to central venous catheter for stability of the disposable infusion device.

Results: The success rate of stable continuous infusion for 50 hours was 93.18%. Three porcine were failed to maintain the continuous infusion. One of them, its extension line was cut off due to agitation and two of them, central venous catheter was out due to loosened fixation and agitation.

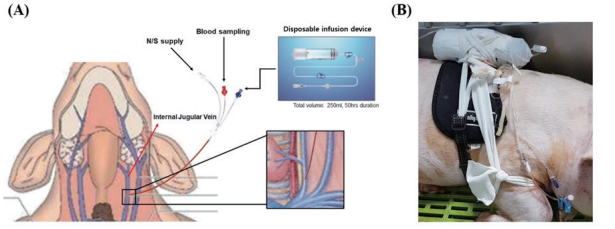

Fig 1. A animal model. (A) Experimental schematic. (B) A large animal model applied continuous intravenous infusion pump.

Conclusions: The disposable infusion device was useful for stable drug injection in a porcine model.

Keywords: Continuous infusion, disposable infusion device, central venous catheter, Porcine

PE-393

Mortality after Hepato-Biliary and Pancreatic Surgery (HBPS) in Queensland, Australia

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General Surgery, QEII Hospital and South Side Health Service, Australia

Aims: HBPS can be associated with significant morbidity and mortality if patients are poorly selected for major surgery. The Queensland Audit for Surgical Mortality (QASM) records all mortalities associated with surgical procedures within Queensland.

Methods: QASM data associated with HBPS over the last 10 years (2007 - 2018) were analysed. Patients who died from multiple trauma or died from other causes unrelated to HBPS disease were excluded in this study.

Results: One hundred and eighteen patients died of 184 deaths that were recorded. Sixty-six were excluded based on the selection criteria as above. AGE DATA: Average age of the patients was 68.3 years Of the 118 there were: 72 males and 46 females 103 were 50 years of age or over (64 M, 39 F) 15 were less than 50 years of age (8M, 7F) SURGICAL PROCEDURES: Liver 24 (20%) Biliary 103 (87%) Pancreas 10 (8.5%) COMORBIDITIES: Cardiac 65 Respiratory 43 Renal 40 COMPLICATIONS: 58 of 118 were identified. 38 required reoperation and 40 had unplanned admission into ICU SURGEONS ASSESSMENT OF SEVERITY OF DISEASE AND RISK OF DEATH PRIOR TO SURGERY WERE: 1. Minimal or small 15 (12.5%) 2. Moderate 31 (26%) 3. Considerable 58 (49%) 4. Expected 12 (10%)

Conclusions: 1. Elderly patients with co-morbidities have a significant risk of death after HBPS 2. The surgeons view of death following surgery was considerable. 3. Patient selection for major HBPS surgery is important to reduce the mortality.

PE-394

A Case of Accessory Cystic Duct with Double Cystic Artery

Dhiraj Saxena

Sawai Man Singh Medical College, Jaipur, Rajasthan, India

Aims: Morphology of accessory cystic artery and biliary apparatus.

Methods: The present study is about a 77 year old cadaver which was dissected during regular dissection classes of undergraduate students.

Results: This case was associated with 2 cystic arteries arising from the right hepatic artery. Both cystic arteries were running parallel to each other. The length of cystic artery 1 and cystic artery 2 were 1.2 cm and 0.9 cm respectively. One accessory duct was found which was coming from the cystic fossa and drained into right hepatic duct.

Conclusions: The knowledge of the anatomy of cystic artery and the biliary apparatus is important for surgeons as injury of these structures may be fatal during cholecystectomy.

Keywords: Cystic artery, Biliary apparatus

PE-395

Case Report Cardiovascular and Acute Kidney Disease Caused by Cardiopulmonary Resuscitation in Blood Sugar

Hari Prasad Dulal

Asunta Medicare Pvt. Ltd., Nepal

Aims: Myocardial dysfunction which lead to tissue hypoperfusionand multiple organ dysfunction it is not a prognostic factor for poor outcome. After spontaneous circulation recovery. Age epinephrine dose, blood glucose and shock status are independent predictors of microvascular and macrovascular complications of diabetes.

Methods: We selected between CVD and AKI share common traditional risk factors such as smoking obesity, hypertension diabetes and dyslipidemia however blood sugar control often under diagnosed and undertreated in patient with CVD and AKI.As clinicians the injurious effects of hyperglycemia are separated into microvascular complication and macrovascular complication. For this reason, patients and physicians should continue to strive for the best possible glucose control.

Results: The Patient 55 years old man had refused diabetic history. This time he was suffered from general weakness for 3 days with polydipsia and polyuria under the impression of hyper osmolar hyperglycemia beside high fever with chills was noted electric cardio version and adenosine was given for par-

oxysmal supraventricular tachycardia and then intubation was perfomed. Initially ventilator with pressure control mode use and high positive end expiratory pressure were used for oxygenation support after sedation and pain control administration beside vasopressor were used for profound shock. Cardiovascular disease (CVD) was suspected and cardiac echo was performed and revealed hyperkinesia at apical and inferior well. We had kept insulin infusion due to persistent hyperglycemia. His condition wasn't improved and shift to tigecycline for atypical pneumonia treatment total hydration with about 4500 L/R plus tetrastarch 500 ml was prescribed. Therefore, oliguria were also noted and poor response to diuresis used Hemodialysis was done due to acute kidney injury (AKI) with oliguria. After above treatment. He was weaned from ventilator on day 15 of cardiac arrest. Now he still has regular insulin continued infusion for diabetic control and keep mechanical ventilator weaning as patient tolerance.

Conclusions: Case Report

PE-396

Metformine and Insuline Resistance Is Associated with Hirsutisum in Unselected Reproductive-Age Nepali Women

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Aims: Hirsutism affects 5_10% of reproductive-age women Nepal and has its clinical importance as cutaneous manifestation of underlying hyperandrogenism although racial and genetic factors are know to play roles in menifestation of hirsutism the pathogenesis of hirsutism is not clear and its cutoff value to dagnose hirsutism was not been determined in Nepal yet. We aimed to investigate the distribution of modified friedman-gallway (mFG) score and determine its cutoff value for defining hirsutism, and to examine its relationship with endocrime and metabolic traits in unselected reproductive-age Nepali women.

Methods: We enrolled 2,139 female volunteers of reproductive age (15_39 years)we recorded mFG scores at 9 different body location (upper lip, chin,chest, arm,upper abdomen lower abdomen, upper back, lower back, and thighs) each in 0-4 scale.75-g oral glucose tolerance test was performed and the homeostasis model assessment of metformin and insulin resistance (HOMA-IR)was calculated.

Results: The cutoff value of mFG score to defiine hirsutism was 6 using a 95th percentile as normal. Of the total subjects,13.5% had mFG scores >3 and 5.8% of women had scores >6.spearmans correlation analysis showed that total testosterone, free testosterone, fasting plasma insulin,and HOMA-IR were positively correlated with Mfg score (all ps <0.05) multiple linear regression analyses showed that fasting plasma insulin and HOMA-IR were independent determinants of mfg score after adjustment for age, body mass index (BMI) and free testosterone (all ps <0.05).

Conclusions: in using a 95th percentile of mfg score as normal, the cutoff value to define hirsutism was 6 in unselected reproductive-age Nepali women. Fasting plasma insulin,metformine and HOMA –IR were positively associated with mfg score after adjustment for age, BMI,and free testosterone. There fore, insulin resistance could participate in the development of hirsutism and estimating insulin resistance would be needed in women with hirsutism.

PE-397

Effect of Millets Flours, Brown Rice, Corn Flours Consumption on Blood Sugar Levels, Lipid Profile and Anthropometric Indices among Selected Politicians and Known to Know Employees in Nepal

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Aims: The study evaluated the effect of Millets flours, brown rice corn flours consumption on the biochemical parameters, used to diagnose diabetes mellitus, Lipid profile,and anthropometric measures among selected politician and known to know employee in Nepal.

Methods: The study was a 6 month dietary intervention trial with participant from the different agencies of the Department of science and technology and Bhaktapur city ASUNTA Medicare pvt ltd. After randomization, the intervention group (n = 28) received and consumed millets flours, brown rice, corn flours daly for 6 months while the control group (n = 29) received and consumed the same variety of white rice daly. A mixed analysis of covariance was politician and employee to compare the observed changes between groups in terms of biochemical parameters,lipid profile, and anthropometic measures from baseline to completion of the intervention change was adjusted for sex,age and respective baseline variables. AP value less then 0.05 was considered statistically significant.

Results: Both groups exhibited similar changes in fasting blood sugar and glycosylated hemoglobin throughout the intervention.A small, positive change in fasting blood sugar was first observed from baseline to midline, followed by a significant improvement (ie reduction) to ward endline. The oppositewas observed for glycosylated hemoglobin, wherein a greater reduction from baseline to midline wes initially observed. On the other hand, the minimal change in postprandial blood sugar among those who consumed millets and corn flours was uniform throughout the intervention while an increase in postprandial blood sugar was first observed among those who consumed white rice,followed by a decrease toward endline. in teams of anthropometric parameters those who consumed brown rice millets flours for 6 months had greater imporovements (ie continuous decline) in the weight, body mass index, and waist circumference as compared to those who consumed white rice, conversely, no imporvement in lipid profile was observed for the brown rice and millets, flours groups.

Conclusions: 6-months consumption of millets flours, brown rice, corn flours was observed to improve blood sugar and anthropometric measures.

PE-398

A Descriptive Study of Clinical Trials Being Conducted in India Related to the Liver Diseases

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Aims: India is one of the attractive destination for clinical trials. It is always advisable to have better data related to all trials happening in country to see if they are as per the disease burden of the country or not. No such synthesized data of clinical trials related to liver diseases is published yet. Aim of this study is to analyse clinical trials related to the liver disease happening in India for various characteristics.

Table 1. Different Characteristics of liver disease related trials registered in clinical Trial Registry of India

Disease Categories	**Frequency**
Acute Hepatitis	6 (4.76)
Alcoholic Hepatitis/ Alcoholic Liver Disease	13 (10.32)
Cirrhosis	2 (1.59)
Acute/Chronic Hepatitis B	51 (40.48)
Hepatitis B with HIV	1 (0.79)
Acute/Chronic Hepatitis C	26 (20.63)
Hepatitis C with Thrombocytopenia	2 (1.58)
Hepatitis A	7 (5.56)
Fatty Liver Disease/Nonalcoholic Steatohepatitis	10 (7.94)
Hepatic Encephalopathy	1 (0.79)
Hepatitis E	1 (0.79)
Hepatocellular Carcinoma	3 (2.38)
Jaundice	2 (1.58)
Kala azar	1 (0.79)
System of therapy	**Frequency**
Allopathic	107 (84.9)
Ayurvedic	5 (3.97)
Herbal	5 (3.97)
Unani	5 (3.97)
Yoga	1 (0.79)
Homeopathic	1 (0.79)
Educational Interventions	1(0.79)
Device	1 (0.79)
Interventions	**Frequency**
Acteoside	1 (0.98)
Adefovir	1(0.98)
Ademetionine	1(0.98)
alb-interferon	1(0.98)
Amphotericin B	1(0.98)
Anesthesia	1(0.98)
Antiviral (Directly acting)	1(0.98)
ART	1(0.98)
Bariatric surgery	1(0.98)
Boceprevir	1(0.98)
Capecitabine	1(0.98)
CLEARLIV	1(0.98)
Daclatasvir	1(0.98)
DEB025	1(0.98)
Durvalumab	2 (1.96)
Eltrombopag	2 (1.96)
Entecavir	1(0.98)
Entecavir plus interferon	1(0.98)
GCSF	1(0.98)
Immunogenecity	1(0.98)
Interferon and Ribavirin	1(0.98)
Ketoconazole	1(0.98)
LJN452	1(0.98)
O'LIVER- T	1(0.98)
Peginterferon alpha 2 b	5 (4.90)
Pegylated interferon alfa-2a and Lamivudine	1(0.98)
Pentoxiphylline	1(0.98)
PF-04136309	1(0.98)
Plasma exchange	1(0.98)
Predisolone	1(0.98)
Prednisolone and Pentoxifylline	1(0.98)
Probiotics	1(0.98)
Saroglitazar	1(0.98)
Selonsertib	2 (1.96)
Sofosbuvir	2 (1.96)
Sofosbuvir and Ribavirin	1(0.98)
Sofosbuvir with Ribavirin	1(0.98)
Sofosbuvir, Ledipasvir and Daclatasvir	1(0.98)
Sofosbuvir/Velpatasvir Fixed Dose Combination	1 (0.98)
Stool Microbiodata	4 (3.92)
Tenofovir	1(0.98)
Tenofovir Alafenamide	3 (2.94)
Tenofovir Disoproxil Fumarate (TDF)	1(0.98)
Tropifexor	1(0.98)
Vaccine	42 (41.17)
Velpatasvir/Sofosbuvir	1(0.98)
Zinc	1(0.98)
ZYH1	1(0.98)
Place of trials	**Frequency**
Multicentric	67 (53.1)
Single centre	59 (46.9)
Recruitment Status	**Frequency**
No recruitment started	29 (23.7)
Completed	45 (36.9)
Recruitment under process	32 (26.2)
Terminated	4 (3.2)
Recruitment not allowed	12(9.8)

Methods: This study is based on publically available data related to the clinical trials in India. India has an online registry of Clinical Trials known as Clinical Trial Registry of India (CTRI). CTRI was searched for trials related to the liver diseases. It was done by using different search terms. Different characteristics of clinical trials were extracted in the preformed extraction form. Various characteristics like year of registration, disease, current status, intervention, sponsor and institutions where the trial is conducted etc were extracted.

Results: Out of total 126 trials, maximum trials were related to the acute/chronic hepatitis B (40.48%), other important disease categories were acute/chronic hepatitis C (20.63%), Alcoholic liver disease (10.32%) and fatty liver/NASH (7.94%). There were 85% trials related to the allopathic drugs followed by Ayurvedic (3.94%), Unani (3.94%) and Herbal drugs (3.94%). In the case of allopathic interventions, most common intervention was vaccines (41.17%). Majority of trials were multicentric (53%). Around 37% trials were completed while 26.2% were open for recruitment. Only one trial was related to the neglected tropical disease.

Conclusions: Majority of clinical trials related to liver disease in India is vaccine trials particularly related to hepatitis B vaccine. Distribution of trials are not per the disease burden.

Keywords: Clinical trials, Liver diseases, India, Disease burden

PE-399

Accessory Liver Fissures: A Case Report and Its Clinical Significance

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Aims: The liver can present a number of congenital anomalies. Knowledge of variations in the external morphology of liver is essential during radiological investigations and surgery. Liver abnormalities are considered to be rare, but their presence can complicate different medical procedure. The knowledge of possible liver anatomy variations can be useful for hepatobiliary surgeons and radiologist, medical practitioners. Accessory liver fissures are a frequent anomaly that can lead to complications during diagnostic and surgical procedures.

Methods: Case report: During regular dissection classes of first year medical undergraduates, accessory liver fissures were observed on the liver surfaces of a male cadaver aged 52 years. Morphology and length of fissures were observed.

Results: The accessary fissures were present on visceral surface and anterosuperior surface of liver. Accessary fissures can be caused by gastric volvulus, portal hypertension or by hypertrophic diaphragmatic bundles and due to defective development. Multiple accessory fissures may mimic pathologic liver nodules on CT and may be associated with diaphragmatic eventration on the chest film.

Conclusions: The incidence of accessory liver fissures is high. Therefore, this should be taken in consideration by health care providers to avoid misdiagnosis. It is important for physicians to be aware of this developmental variation.

Keywords: Accessory liver fissure, Hepatobiliary, Liver

PE-400

Liver Diseases in Myanmar

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Aims: There is a scarcity of Myanmar incidence, prevalence and mortality data relating to liver diseases which is neglected health problem. We aimed to describe epidemiology of liver diseases and related risk factors.

Methods: In this study, we reviewed several data sources including peer-reviewed literatures, grey literatures (such as government reports), government websites and international sources were also included such as Global Burden of Disease Study, WHO and INGOs reports.

Results: Although high prevalence of anti-HAV IgG positivity in adult population, there is no available published literature. Overall prevalence of HBV and HCV in general population is 6.51% and 2.65%. HIV/HBV, HIV/HCV and HIV&HBV/HCV co-infection rate are 2.2%, 20.1% and 20.7% respectively. Most prevalence of HBV genotype was genotype C (77%) followed by genotype A (8%). Genotype 3 (33 - 80%) HCV is the most frequently encounter infection followed by genotype 6 (16-60%), 1 (9 -25%) and 2. Hepatitis D infection has not been found in 278 blood samples of HBsAg positive healthy carriers and blood donors. Seroprevalence of anti-HEV IgG is was 32-35.1%. The age prevalence of anti-HEV IgG was 3% in for patients younger than 20 years and 30% or more for patients 20 years or older. Prevalence of liver cirrhosis and liver cancer are increasing and which contributed 5.65% and 1.1% of total death respectively. The underlying etiologies of liver cancer cases were HBV (43 -60%) and HCV (29 – 35%). There is no available published literatures about alcohol related liver diseases and fatty liver disease.

Conclusions: This study shows that is calls for public health, Hepatology community, stakeholders and policy marker to coordinate effort to implement the measure of true burden of liver diseases and effective strategies for prevention to lessen the liver disease related morbidity, mortality and financial impact including direct and indirect cost related to individual health.

Keywords: HBV, HCV, HCC, Epidemiology

PE-401

Complementary and Alternative Medicine (CM) Deterioration of Chronic Kidney Patients in Nepal

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Aims: All over the Nepal many Patient of Kidney Consume alternative and Complimentary drugs with or without allopathic medicine There are Few case reports which indicates deterioration of various Kidney function because of the Presence of heavy metals in this Preparations. No large scale study is available to check this hence study was planned with the primary aim of evaluating use complementary and alternative medicine and deterioration of kidney function in chronic kidney patients

Methods: This is a small cross sectional study out patient department of clinic at ASUNTA Medicare Hospital all patients coming for the treatment kidney disease were offered to participate in the study. Willing participants were interviewed for various parameters including current and past use of CM.blood reports of these patients were obtained from online system of the institution creatinine was considered.The marks of kidney function test deterioration descriptive statistics was reported in the form of frequency and percentages Odds ratio for all the parameters for kidney function deterioration was calculated using poisons regression by using SPSS Vs 17.

Results: Out of all the variables only not having the hypertension was significantly associated with the protection against deteriorated kidney functions (OR = 0243(95%cl 0.07-083)no other factors like current and past use of CM age gender history of kidney disease in family blood test (glomerular filtration rate) were associated with the deterioration of kidney function

Conclusions: In this study we could not found any statistical association between the consumption of CM and deterioration of kidney function in chronic kidney disease patients.

PE-402

Lipidogram in Patients with Type2 Diabetes Mellitus Infected with Hepatitis B and C Viruses

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Aims: Study lipid metabolism in patients with type2 diabetes mellitus (DM) depending on the infection with Hepato tropic viruses (HBV, HCV).

Methods: 96 patients with diabetes mellitus (men-24 (24.2%) Average, Age (58.0±11.74) years. were examined. The Standard markers of viral Hepatitis B and C (EIA), the main Indices of the Lipidogram (Total cholesterol, LNOP, LDL, HDL Triglycerides, TG, rogenity, Spacecraft).

Results: According to the Results of the Test for markers of viral Hepatitis B and C, all patients were divided into two groups: infected with HVB/HCV (group 32.3%) and Uninfected (group 2.67.7%) in a comparative analysis, it was found that in HBV/HCV infected patients with diabetes, the levels of almost all parameters were statistically significantly lower than those of uninfected patients. Thus, the median of total cholesterol in the first group was 5.5 mmol/l, in the second 6.0 mol/l (P = 0.007), median TG content-1.5 and 2.5 mmol/l (P = 0.002); LDL-2.5 and 3.6 mmol/l (P = 0.002); PLDL-07 and 1.1 mmol/l (P = 0.044); KA-2.7 and 4.2 (P = 0.018). The level of HDL was the same in patients of both groups and was 1.2 (1.0-104) mmol/l, respectively. Further, patients of the 1st group (HBV/HCV-infected) were divided in to two subgroups. The first group included patients with a normal level of aminotransferases, the second with an increased level of aminotransferases.

Conclusions: The Obtained results testify to the possible role of chronic Hepato tropic viral infection in the violation of the function state of the liver and lipid metabolism in patients with type2 diabetes mellitus

PE-403

A Case of Hepatitis A Associated with Subchorionic Hematoma during Pregnancy

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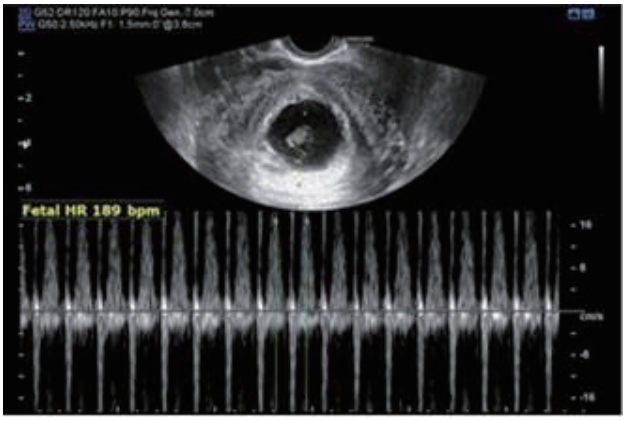
Aims: Hepatitis A virus (HAV) is an enterovirus of the family Picornaviridae that is transmitted primarily via the fecal-oral route. Most affected age is in 20-40 years and most viral hepatitis A patients have experienced benign course without complication. Moreover, HAV infection is not associated with severe outcomes or complications during pregnancy. But also maternal-infant HAV transmission is thought to be uncommon. Recently, we introduce a case that pregnant woman with HAV associated with subchorionic hematoma

Methods: This review is based on medical records including lab data, sonographic view.

Results: A 36-year-old woman was at 8 weeks with Gestational age (1-0-3-1) and she was followed local obstetrics clinic. She represented to our emergency department with fever lasting 2 days and vaginal bleeding. Vaginal sonographic examination at our OBGY department revealed that she had subchorionic hematoma. She was also presented vaginal bleeding about 35cc. We examined emergent vaginal ultrasonography and hematoma was occurred in Cervical Os. Considering her's abortion History, We doubted lupus and antiphospholipid antibody syndrome. In our laboratory data, Anti-nucleic acid antibody, Anti double strand DNA Ab, and Anti PL IgM/G were all negative. Especially, in our laboratory data, the mild elevation of total bilirubin and striking elevation of liver enzymes were observed. Moreover, HAV IgM was positive and acute hepatitis A was confirmed. As a result of abdominal ultrasonography, she had mild hepatomegaly and fatty liver and diffuse edematous wall thickening of Gallbladder. After consulting to department of obstetrics, they recommend that if patient does not represent vaginal bleeding & abdominal pain, observe the status and follow up in outpatient department. We planned that the patient will be discharged and followed up at outpatient department.



Conclusions: Symptomatic HAV patients experiencing a fulminant course of illness that may result in death or emergent liver transplantation with advanced or comorbid conditions were less than 1%. Most HAV patients have benign course without complication. Recently, according to epidemiologic surge of HAV in Daejeon, South Korea, we doubt that this patient could have acute hepatitis A infection, and as a lab result, definite diagnosis is HAV. According to domestic journal, the case that involving preterm contraction and subsequent preterm labor and one case of the fetus presenting with ascites and intraabdominal calcifi-

cation[1)]. On the other hand, premature contractions, placental separation, premature rupture of membranes, and vaginal bleeding[2)]. Therefore, we report that it is the first case of presenting subchorionic hematoma in pregnant woman with HAV.

Keywords: HAV, Pregnancy, 8 weeks, Subchorionic hematoma

PE-404

Prognosis and Risk Factors of Acute Viral Hepatitis D in Mongolia

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Aims: A decline in hepatitis D virus (HDV) occurrence was described in Mongolia. Hepatitis D virus (HDV) infection is considered to cause more severe hepatitis such as liver cirrhosis and HCC.Mongolia has the highest prevalence (> 15%) of HCV, (> 10%) HBV infection and HDV 75% of HBsAg carriers

Methods: A total of 86 patients with acute viral hepatitis D were enrolled and their data collected 2016-2017. The study was approved by the Ethics Committee at the Health Sciences University of Mongolia and the Health Ethics Committee of the Ministry of Health of Mongolia.

Results: The mean age of patients was 29.7±7.17. 52(60,4%) of them were males and 34(39.6%) were females. Risk factors were unprotected sexual contact 41(47.67%), dental treatment 11(12.8%), tattoo 8(9.3%), admit hospital 42(48.83%), surgeon13(15.1%), acupuncture 12(13.9%), share with nail knife74(86%) and family contacts with viral hepatitis B 23(26.7%). Anti-HDV IgM and anti-HD total Ab tests were both positive in 34/86 samples, anti HDV IgM was the only positive delta marker in 65/86 samples and anti-HD total Ab was the only marker in 61/86 samples. During follow-up, three of 5 (4.9%) patients with co D infection showed HBsAg loss and 58 patients with super D infection (100%) showedpersistent hepatitis B and D viremia.

Conclusions: Risk factors for hepatitis D virus infection were unprotected sexual contact, admited hospital, share with nailknifeand family contacts with viral hepatitis B. During follow-up, three of 5 (60%) patients with co D infection showed HBsAg loss and 58 patients with super D infection (100%) showed persistent hepatitis B and D viremia.

Keywords: HDV, Mongolia, Acute viral hepatitis

PE-405

Analysis of Chemical Composition of a Single Cellular Lipid Droplet in Liver Cells

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Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder characterized by excessive accumulation of lipids, mainly triglycerides (TG) in the form of lipid droplets (LD). Increase free fatty acids (FA) is one of the important mediators to stimulate fatty changes in the liver. The chemical composition of LD and its association with types of FA inducing LD formation is not well studied. Therefore, the aim of this study is to determine chemical composition and profiling of TG and phosphatidylcholines (PC) in LD in HepG2 cells induced by oleic (FA18:1), linoleic (FA18:2), and linolenic acid (FA18:3).

Methods: LD were induced in HepG2 cells by incubating cells in DMEM medium supplemented with varying concentration of FA18:1, FA18:2, FA18:3, and FA extracted in human plasma for 48 hr followed by washing of the cells with ammonium formate solution. Single LD sample was isolated from the cells using 3D mobile manipulator visualized under invert microscope. The aspirated LD is analyzed by LTQ Orbitrap mass spectrometry equipped with nano-electrospray ionization.

Results: Treatment of cells with FA stimulated the formation of numerous LD within a cell with size ranging from 1–8 μm. TG50:1, TG50:2, TG52:2, TG52:3, TG52:4, TG54:3, TG54:4, TG54:5, and TG54:6 were the major TG found in LD. The relative concentration of TG depends on the type of FA that induce the LD formation. Cells treated with FA18:1 is associated with significant increase in the content of TG50:1, TG52:1, TG52:2, TG54:2, and TG54:3 whereas LD in the cells treated with FA18:2 showed increase content of TG52:4, TG54:5, and TG54:6. The relative concentration of PC34:1, PC36:1 and PC36:2 is higher in the LD of cells treated with FA18:1.

Conclusions: Chemical composition of LD was determined in HepG2 cells. The chemical compositions of TG and PC depend on the type of FA used to induce the LD formation.

Keywords: HepG2 cells, Lipid droplets, Triglycerides, Fatty liver

PE-406

Effects of Chronic Kidney Disease on Liver Enzymes Activity during Pre and Post Hemodialysis

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Aims: The aim of this study was to find the activity of liver enzymes ALT, AST, ALP, and GGT in the patient's serum before and after dialysis in chronic kidney diseases as compared to healthy control group.

Methods: This is a case-control study including 68 cases with chronic kidney disease coming for hemodialysis at dialysis

centers and 55 Healthy individuals as control, conducted at Department of Clinical Biochemistry, Manipal Teaching Hospital, Phoolbari, Pokhara, Nepal from 2016 to 2017. The informed consent was taken and Three ml of the venous blood was collected and kept in 12''x75'' gel tubes. Serum samples were used for the analysis of Serum Urea and Creatinine, liver enzymes Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP) and Gamma Glutamyl Transferase (GGT) using (Erba Mannheim) XL- 300 Chemistry autoanalyzer. Pearson's bivariate correlation analysis and ANOVA was used to correlate variables between the controls and cases. $P < 0.05$ was considered to be statistically significant.

Results: Urea and creatinine levels were significantly higher in both pre-hemodialysis and post-hemodialysis as compared to healthy controls with *P* value ($P < 0.000$). AST levels were significantly lower in both pre hemodialysis (19.32 ±10.80) and post-hemodialysis (17.66 ± 8.84) as compared to healthy controls (28.32± 9.68), ($P < 0.000$). No statistically significant difference was observed between the AST values of Pre and Post hemodialysis ($P < 0.183$). Similarly, serum ALT levels were also significantly lower in both Prehemodilysis (26.88± 41.97) and Posthemodilysis (21.96± 11.76) as compared to Healthy control (36.50± 16.95) ($P < 0.015$). No statistically significant difference was observed between the ALT values of Per and Post hemodialysis ($P < 0.353$). On the other hand serum, ALP levels were significantly higher in Prehemodilysis (123.96±66.80) and Posthemodilysis (115.81±65.83) as compared to healthy control (90.65±26.19) ($P < 0.006$). No statistically significant difference was observed between the AL*P* values of Pre and Post hemodialysis ($P < 0.449$). Moreover, serum GGT levels were significantly higher in Prehemodilysis (79.60 ± 84.39) and Posthemodilysis (75.80 ± 79.77) as compared to healthy control (35.18± 27.81) ($P < 0.001$). No statistically significant difference was observed between the GGT values of Pre and Post hemodialysis ($P < 0.788$).

Conclusions: Our results showed differences in the level of liver enzymes in pre and post hemodialysis in Chronic kidney disease.

Keywords: Liver enzymes, Chronic kidney diseases, Hemodialysis, GGT

PE-407

Lymphoid Hyperplasia of the Liver Mimicking Hepatocellular Carcinoma: A Case Report

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Aims: Lymphoid hyperplasia of the liver is uncommon and benign mass like lesion. It is difficult to differentiate between the lymphoid hyperplasia and hepatoma without pathology.

Methods: A 68-year old woman was admitted for evaluating the liver tumor. Heptobiliary computed tomogram showed a 1.3 centimeter sized round low attenuating lesion in segment 7 and 8 area of the liver. MRI showed a 1.4 centimeter sized nodular lesion in S8 of the liver which is T1 low and T2 high signal intensity,weak enhancement with rim enhancement, portal and delayed washout, and diffusion restriction defect in hepato-biliary pancreatic images suggesting probable hepatocellular carcinoma.

Results: She underwent wedge resection of the S7 area of the liver. Pathology showed lymphoid hyperplasia in liver with well demarcated yellow colored lesion.

Conclusions: So we reported a case report and short literature review.

PE-408

Liver Enzymes Activity in Patients with Chronic Kidney Disease on Hemodialysis

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Aims: Chronic kidney disease (CKD) is a condition in which kidney is damaged.The common liver diseases in CKD patients are hepatitis B and C. So, the aim of study was to find activity of liver enzymes in patients with CKD on hemodialysis in compare to healthy control.

Methods: In this study a total of 56 patients with chronic kidney disease on hemodialysis at dialysis centers and 50 Healthy individuals as control were enrolled and study was conducted at Department of Biochemistry, Manipal Teaching Hospital, Pokhara, Nepal. The informed consent was taken and 5 ml of the venous blood was collected in plain tubes. Serum was used for the analysis of urea, creatinine, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP) and Gamma Glutamyl Transferase (GGT) using Vitrous 350 chemistry auto analyzer. Student t test was used to correlate variables between the controls and cases. $P < 0.05$ was considered to be statistically significant.

Results: The serum level of urea and creatinine were significantly higher in CKD patients as compared to healthy controls with *P* value ($P < 0.001$). The serum levels of ALT were significantly lower in CKD patients on hemodialysis (24.12± 13.97) as compared to healthy control (35.41± 15.73) ($P < 0.016$). Similarly, AST levels were significantly lower in CKD patients (18.31 ±9.25) as compared to healthy controls (27.91± 8.75) ($P < 0.001$). The serum levels of ALP were significantly higher in CKD patients (119.17±65.72) as compared to healthy control (91.58±25.28) ($P < 0.005$). Similarly, serum GGT levels were significantly higher in CKD patients (78.25± 14.39) as compared to healthy control (34.56± 17.81) ($P < 0.001$).

Conclusions: This study showed differences in level of liver enzyme activity in CKD patients on hemodialysis. The activity of ALT and AST were showed low but activity of ALP and GGT were showed high.

Keywords: Liver Enzymes, Chronic Kidney Disease, Hemodialysis, Nepal

PE-409

Diagnostic Performance of Serum Asialo-α1-Acid Glycoprotein for Advanced Liver Fibrosis or Cirrhosis in Patients with Chronic Hepatitis B or Nonalcoholic Fatty Liver Disease

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Aims: The utility of asialo-α1-acid glycoprotein (AsAGP) for assessing the fibrotic burden is unknown. We investigated the diagnostic performance of the AsAGP level for advanced liver fibrosis or cirrhosis in patients with chronic hepatitis B (CHB) or nonalcoholic fatty liver disease (NAFLD).

Methods: From July to December 2018, 48 patients with CHB and 75 with NAFLD were recruited prospectively. Transient elastography was used as the reference standard for liver fibrosis, and the cutoff liver stiffness (LS) values were defined as 10.0 kPa for ≥ F3 and 12.0 kPa for F4 in CHB patients and 9.0 kPa for ≥ F3 and 11.8 kPa for F4 in NAFLD patients.

Results: To predict stage ≥ F3 and F4 fibrosis, the areas under the receiver operating characteristic curves of the AsAGP level were 0.788 (95% confidence interval [CI], 0.647–0.930; P = 0.005) and 0.825 (95% CI, 0.674–0.976; P = 0.004), respectively, in patients with CHB. The cutoff AsAGP levels in patients with CHB that maximized the sum of the sensitivity and specificity values were 1.31 (sensitivity 100.0%, specificity 52.6%) and 1.55 (sensitivity 75.0%, specificity 80.0%), respectively. In contrast, the AsAGP level did not differ significantly according to fibrosis stage in patients with NAFLD (all P > 0.05 between the stages).

Conclusions: The AsAGP level showed acceptable diagnostic accuracy in predicting advanced liver fibrosis and cirrhosis in patients with CHB but not in those with NAFLD. Further studies are needed to validate the diagnostic performance of the AsAGP level in patients with NALFD.

Keywords: Asialo-α1-acid glycoprotein, Liver fibrosis, Hepatitis B, Nonalcoholic fatty liver disease

PE-410

SGOT, SGPT and Alkaline Phosphatase among Suspected Liver Patients Attending Pyuthan District Hospital, Pyuthan, Nepal

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Aims: Serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-Pyruvate transaminase (SGPT) and alkaline phosphatase are reasonably sensitive indicators of liver damage or injury from different types of diseases or conditions. The study aimed to determine the level of SGOT, SGPT and alkaline phosphatase; and SGOT/SGPT ratio among suspected liver patients attending Pyuthan District hospital of Nepal.

Methods: Blood samples were collected from suspected liver patients visiting *Pyuthan* hospital. The samples were collected from August, 2018 to February 2019. Enzyme kinetics method was used to process the serum samples. Descriptive statistics and chi-square test were computed at 5% level of significance

Results: Of total 100 suspected liver patients, 60.9% patients had high SGOT, 41.8% had high SGPT and 60.9% had high alkaline phosphatase. There was significant difference in the prevalence of high SGOT across sex (P < 0.05). The prevalence of high SGOT was higher among males (68.1% Vs 4 8.8%). Regarding SGPT and high alkaline phosphatase, there was no significant difference in the prevalence of high SGPT across sex. Ethnicity was also statistically associated with high SGOT in the study (P < 0.05); it was lowest among Brahmin ethinic group and highest among Janajati group. However, there was no statistical association of high SGPT and high alkaline phosphatase with ethnicity. Age group was also associated with alkaline phosphatase. The mean SGOT /SGPT ratio was 1.66 (±.47) among the patients.

Conclusions: The study revealed high prevalence of SGOT, SGPT and alkaline phosphatase; and high SGOT/ SGPT ratio among suspected liver patients attending Pyuthan hospital of Nepal.

Keywords: SGOT, SGPT, ALP, Nepal

PE-411

Conservative Management of Traumatic Acute Intramural Hematoma of Duodenal 2nd and 3rd Portion: A Case Report and Review of Literature

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Aims: Traumatic intramural duodenal hematoma (IMDH) is a rare disease occurring usually in children. The treatment modality varies according to the symptoms, clinical manifestations and complications represented by patients. Here we introduce a case of a young man with a IMDH caused by traumatic event, who has been treated nonoperatively for 3 weeks and has been discharged with no specific complications.

Methods: A 17-year-old male patient who had been vomiting and had poor oral intake for 4 days was admitted to our institution. We decided to take MRI scan. The source of the GI symptoms revealed in MRI scan was found to be the acute intramural hematoma of duodenal 2nd and 3rd portion.

Results: Total parenteral nutritional therapy with adequate fluid replacement and nil per os (NPO) was applied. The patient was

able to take some sips of water or small bites of fruits with no abdominal discomfort or vomiting. The patient resolved in symptoms of vomiting and poor oral intake, we decided to further follow up the CT scan after 1 month of discharge. 7 weeks after the admission, the intramural hematoma located in 2nd to 3rd portion of duodenum has completely resolved with very minimal periduodenal fluid left.

Conclusions: Patient with traumatic acute intramural hematoma of duodenal 2nd and 3rd portion have excellent clinical outcomes with conservative therapy.

PE-412

Epidemiology of Wilson's Disease in South Korea: A Population-Based Study Using the National Health Insurance Database

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Aims: Wilson's disease is an autosomal recessive disorder that leads various clinical features such as hepatic, neurologic or psychiatric symptoms. However, there were only a few population-based studies on the epidemiology of Wilson's disease. Thus, we aimed to investigate the epidemiology Wilson's disease using National Health Insurance database in Korea.

Methods: The patients with Wilson's disease were identified by the International Classification of Diseases (ICD)-10 code. We used National Health Insurance database from 2010 to 2016. We analyzed the incidence rate, prevalence, and clinical symptoms of Wilson's disease.

Results: A total 1,333 patients were identified. The average annual incidence rate was 4.40 per million person-years. The prevalence was 48.10 per million. Among them, 988 (74.1%) had hepatic symptoms, 510 (38.3%) had neurologic symptoms, and 601 (45.1%) had psychiatric symptoms. Before the diagnosis of Wilson's disease, 350 (26.3%) had neurologic symptoms and 427 (32.0%) had psychiatric symptoms. Hepatocellular carcinoma (HCC) was diagnosed in 195 (14.6%) patients and the mean age was 33.73±17.03 years old. Among them, 87 (44.6%) were diagnosed with HCC before Wilson's disease was diagnosed. D-penicillamine, trientine or zinc acetate were administered in 465 (34.9%) patients, but did not influence the mortality. The age, fulminant hepatitis, liver cirrhosis and HCC were related with the fatal prognosis ($P < 0.05$). Amon 1,333 patients, 56 underwent liver transplantation. The survival rates of them were 100, 95.8, 95.8 and 92.3% at 1, 2, 3, and 4 years.

Conclusions: This is the first epidemiological study of Wilson's disease using population-based database in Korea. Many patients showed neurologic and psychiatric symptoms before Wilson's disease was diagnosed. The prognosis was related with age, fulminant hepatitis, liver cirrhosis and HCC.

Keywords: Wilson's disease, Incidence, Prevalence

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