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CMH Clinical and Molecular Hepatology

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

The 22nd Annual Meeting of the Korean Association for the Study of the Liver
The Korean Association of HBP Surgery Symposium
The 19th 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 the organizing committee of The Liver Week 2016, we are delighted to welcome you to The Liver Week 2016 which will be held from June 16-18, 2016 at the Grand Hyatt Hotel in Incheon, Korea.

During this meeting, we plan to provide the cutting edge knowledge and opinions on acute and chronic liver diseases under the subject, 'Next Wave in Hepatology'. With state-of-the-art lectures and presentations followed by in depth discussions among lecturers and attendees, we hope that all the participants from the fields of clinical medicine and basic science to associates from pharmacy and medical equipment, who strive to achieve one goal, "eradication of the liver diseases", will be able to share their valuable knowledge and opinions.

The Liver Week 2016 will be held by the Korean Association for the Study of the Liver (KASL), jointly with the Korean Association of HBP Surgery (KHBPS), the Korean Liver Cancer Association (KLCA) and the Korean Liver Transplantation Society (KLTS), enabling the attendees to effectively learn how professionals of each field take clinical approaches and understand various chronic liver diseases within the limited time.

We thank you for being a part of this conference and hope you leave with wonderful memories of your stay in Incheon.

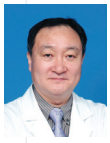
Yours sincerely,

Kwan Soo Byun
President
The Liver Week 2016

Yung Sang Lee
Chairman
The Liver Week 2016

Kyung-Suk Suh
Vice President
The Liver Week 2016

Soon Ho Um
Vice President
The Liver Week 2016



Jae-Won Joh
Vice President
The Liver Week 2016

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

Organizing Committee

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Congress President	Kwan Soo Byun			
Congress Vice President	Kyung Suk Suh	Soon Ho Um	Jae Won Joh	
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	In Seok Choi	Jong Young Choi	Jin Seok Heo	Shin Hwang

Program at a Glance

DAY 1 Thursday, June 16, 2016

■ WEST TOWER ■ EAST TOWER

K : Session in Korean

	ROOM AB	ROOM D	ROOM AB
08:00	* Postgraduate Course: Recent Update of Chronic Liver Disease (CLD) Treatment		
09:00	PG1. Management of Viral CLD, LC, and HCC (*K) (08:30-10:10)		Basic Science Workshop 1 (08:30-10:10)
10:00	Coffee Break (10:10-10:30)		
11:00	PG2. Management of Non-viral CLD (*K) (10:30-12:10)		Basic Science Workshop 2 (10:30-12:10)
12:00	Luncheon Symposium 1 [by Yuhan] (12:10-13:10)		Luncheon Symposium 2 [by BMS] (12:10-13:10)
13:00	PG3. Diagnosis and Management of Metabolic Complications in CLD (*K) (13:10-14:50)		Clinical Science Methodology Workshop 1 (13:10-14:50)
14:00	Coffee Break (14:50-15:10)		
15:00	PG4. Organ Dysfunction in CLD (*K) (15:10-16:50)		Clinical Science Methodology Workshop 2 (15:10-16:50)
16:00		CMH Workshop Closed Meeting (16:30-20:00)	
17:00			
20:00			

WEST TOWER

Room AB [B1]

08:30-10:10	PG1: Management of Viral Chronic Liver Disease, Liver Cirrhosis, and Hepatocellular Carcinoma [*K]	*Heon Ju Lee (Yeungnam Univ.), Byung-Ho Kim (Kyung Hee Univ.)*
08:30-08:55	Chronic Hepatitis C Treatment: KASL Clinical Guidelines	*Jung Il Lee, Yonsei Univ.*
08:55-09:20	Hepatitis B Virus Treatment	*Byung Seok Lee, Chungnam National Univ.*
09:20-09:45	Management of Advanced Hepatocellular Carcinoma	*Jeong-Hoon Lee, Seoul National Univ.*
09:45-10:10	Treatment of Portal Hypertension Related Complications	*Yeon Seok Seo, Korea Univ.*
10:10-10:30	Coffee Break	
10:30-12:10	PG2: Management of Non-viral Chronic Liver Disease [*K]	*Jin Mo Yang (The Catholic Univ. of Korea), Won-Choong Choi (Inje Univ.)*
10:30-10:55	Management of Alcoholic Liver Disease	*In Hee Kim, Chonbuk National Univ.*
10:55-11:20	Treatment for Non-alcoholic Fatty Liver Disease	*Byoung Kuk Jang, Keimyung Univ.*
11:20-11:45	Treatment of Autoimmune Hepatitis and Primary Biliary Cirrhosis	*Kyung-Ah Kim, Inje Univ.*
11:45-12:10	Vaccinations for Adults with Chronic Liver Disease	*Nam Su Ku, Yonsei Univ.*
12:10-13:10	Luncheon Symposium 1 [by Yuhan]	
13:10-14:50	PG3: Diagnosis and Management of Metabolic Complications in Chronic Liver Disease [*K]	*Joon-Yeol Han (The Catholic Univ. of Korea), So Young Kwon (Konkuk Univ.)*
13:10-13:35	Diagnosis and Management of Metabolic Syndrome and Obesity in Chronic Liver Disease	*Sin Gon Kim, Korea Univ.*
13:35-14:00	Diagnosis and Management of Osteoporosis and Vitamin D Deficiency in Chronic Liver Disease	*Sun Wook Cho, Seoul National Univ.*
14:00-14:25	Diagnosis and Management of Dyslipidemia in Chronic Liver Disease	*Eun Mi Lee, Wonkwang Univ.*
14:25-14:50	Diagnosis and Management of Diabetes Mellitus in Chronic Liver Disease Focusing on Fatty Liver	*Soo Lim, Seoul National Univ.*
14:50-15:10	Coffee Break	
15:10-16:50	PG4: Organ Dysfunction in Chronic Liver Disease [*K]	*Young Woo Kang (Konyang Univ.), Jong Eun Yeon (Korea Univ.)*
15:10-15:35	Diagnosis and Management of Heart Failure in Chronic Liver Disease	*Jong-Chan Youn, Hallym Univ.*
15:35-16:00	Diagnosis and Management of Thyroid and Adrenal Dysfunction in Chronic Liver Disease	*Young Joo Park, Seoul National Univ.*
16:00-16:25	Diagnosis and Management of Renal Dysfunction in Chronic Liver Disease	*Jeonghwan Lee, Hallym Univ.*
16:25-16:50	Sepsis in Cirrhosis - Perspective by New Sepsis Guidelines 2016	*Sang-Bum Hong, Univ. of Ulsan*

EAST TOWER

Room AB [2F]

08:30-10:10	**Basic Science Workshop 1** Intra and Extracellular Vesicle: Cell to Cell Cross Talk in the Liver	*Dae-Ghon Kim (Chonbuk National Univ.), Kyun-Hwan Kim (Konkuk Univ.)*
08:30-09:10	Exosome	*Yong Song Gho, POSTECH*
09:10-09:30	Exosome and Liver Disease	*Yong-Han Paik, Sungkyunkwan Univ.*
09:30-10:10	Role of Autophagy in Liver Injury	*Wen-Xing Ding, Univ. of Kansas*
10:10-10:30	Coffee Break	
10:30-12:10	**Basic Science Workshop 2** Intra and Extracellular Vesicle: Cell to Cell Cross Talk in the Liver	*Kwan Sik Lee (Yonsei Univ.), Jin-Wook Kim (Seoul National Univ.)*
10:30-11:10	Autophagy in Chronic Viral Hepatitis	*Seong-Jun Kim, Korea Research Institute of Chemical Technology*
11:10-11:50	Regulation of Inflammasome Signaling and Its Potential Link to Metabolic Disorders	*Je-Wook Yu, Yonsei Univ.*
11:50-12:10	Inflammasome in Liver Disease	*Jong Eun Yeon, Korea Univ.*
12:10-13:10	Luncheon Symposium 2 [by BMS]	
13:10-14:50	**Clinical Science Methodology Workshop 1** Real World Experience from Expert	*W. Ray Kim (Stanford Univ.), Jung-Hwan Yoon (Seoul National Univ.)*
13:10-13:50	MELD: From an Idea into a Practice	*W. Ray Kim, Stanford Univ.*
13:50-14:20	RCT: From an Idea into a Practice	*Young-Suk Lim, Univ. of Ulsan*
14:20-14:50	Cohort Study: From an Idea into a Practice	*Jeong Won Jang, The Catholic Univ. of Korea*
14:50-15:10	Coffee Break	
15:10-16:50	**Clinical Science Methodology Workshop 2** Real World Experience from Expert	*Kengo Yoshimitsu (Fukuoka Univ.), Han Chu Lee (Univ. of Ulsan)*
15:10-15:40	From an Idea into a New Device: MR Elastography	*Kengo Yoshimitsu, Fukuoka Univ.*
15:40-16:10	From an Idea into a New Drug: Oltipraz	*Yoon Jun Kim, Seoul National Univ.*
16:10-16:50	How to Prove Cost-effectiveness in My Research	*Jeonghoon Ahn, Ewha Womans Univ.*

Program at a Glance

DAY 2 Friday, June 17, 2016

■ WEST TOWER ■ EAST TOWER

K : Session in Korean

	ROOM AB	ROOM C	ROOM D	ROOM A	ROOM B	ROOM C	ROOM D	ROOM E	ROOM F
07:00							EMW 1 [*K] HBV (07:00-08:00)	EMW 2 HCV (07:00-08:00)	
08:00	Opening Ceremony (08:15-08:30)								
09:00	Symposium 1 HCV (08:30-09:50)			KLTS Symposium 1 [*K] (08:30-09:50)	KASL-KLCA Joint Symposium (08:30-09:50)				
10:00	Coffee Break (09:50-10:10)								
11:00	Plenary Session 1 (10:10-12:10)			KLTS Symposium 2 [*K] (10:10-12:10)	Multidisciplinary Approach to Patients with TACE Failure (10:10-11:20)				
12:00					KLCA General Meeting (11:20-12:10)				
13:00	Luncheon Symposium 3 [by BMS] (12:10-13:10)		Press Conference (12:10-13:10)	Luncheon Symposium 4 [by Dong-A ST] (12:10-13:10)	Luncheon Symposium 5 [by Bayer] (12:10-13:10)				
14:00	Special Lecture 1 (13:10-13:40)	Health Policy Forum [*K] (13:10-14:40)			KLCA-KHBPS Joint Symposium [*K] (13:10-15:15)				KLTS Coordinator Session [*K] (13:10-14:10)
15:00	Clinical Hepatology Update [*K] (13:50-15:30)		Free Paper 1 HBV, Clinical (13:50-15:30)	Free Paper 2 HCV, Clinical (13:50-15:30)	Korea Central Cancer Registry [*K] (15:15-15:30)		Free Paper 3 NAFLD, Clinical (13:50-15:30)		
16:00	Coffee Break & Poster Oral Presentation (15:30-16:30)								
17:00	Special Interest Group Symposium 1 NAFLD (16:30-18:10)		Free Paper 4 HBV, Clinical (16:30-18:10)	Free Paper 5 HCV, Clinical (16:30-18:10)	Emerging Therapies for HCC [*K] (16:30-17:30)		Free Paper 6 Liver Cirrhosis, Clinical (16:30-18:10)		Free Paper 7 Liver Transplantation (16:30-18:10)
18:00		Faculty Dinner (18:00-20:30)							
19:00									

The Korean Association for the Study of the Liver (KASL) The Korean Liver Transplantation Society (KLTS)
The Korean Association of HBP Surgery (KHBPS) The Korean Liver Cancer Association (KLCA)

WEST TOWER — Room AB [B1]

08:30-09:50	**Symposium 1** Hepatitis C Virus	*Mark Sulkowski (Johns Hopkins Univ.), Young-Hwa Chung (Univ. of Ulsan)*
08:30-08:50	Appropriate Application of Direct Acting Antivirals	*Mark Sulkowski, Johns Hopkins Univ.*
08:50-09:10	Current Strategy for Chronic Hepatitis C Treatment in Korea	*Sook-Hyang Jeong, Seoul National Univ.*
09:10-09:30	Towards IFN-free Treatment: DCV+ASV for Genotype 1	*Sang Hoon Ahn, Yonsei Univ.*
09:30-09:50	Management of Direct Antiviral Agent Failures	*Maria Buti, Hospital Universitari Vall d'Hebron*
09:50-10:10	Coffee Break	
10:10-12:10	**Plenary Session 1**	*1-1. W. Ray Kim (Stanford Univ.), Soon Ho Um (Korea Univ.)* *1-2. Byung Chul Yoo (Konkuk Univ.), Jae-Won Joh (Sungkyunkwan Univ.)*
12:10-13:10	Luncheon Symposium 3 [by BMS]	
13:10-13:40	**Special Lecture 1**	*Yung Sang Lee (Univ. of Ulsan)*
	Acute Kidney Injury in Cirrhosis	*Florence Wong, Univ. of Toronto*
13:50-15:30	**Clinical Hepatology Update** (*K)	*Haak Cheoul Kim (Wonkwang Univ.), Young Oh Kweon (Kyungpook National Univ.)*
13:50-14:10	Clinical Hepatology Update: Changes of DDLT Waiting Priority in Korea	*Myoung Soo Kim, Yonsei Univ.*
14:10-14:30	Diagnosis of Sub-centimeter Sized Hepatocellular Carcinoma	*Young Kon Kim, Sungkyunkwan Univ.*
14:30-14:50	Nonalcoholic Steatohepatitis: Diagnosis and Treatment Update	*Dae Won Jun, Hanyang Univ.*
14:50-15:10	Hepatitis C Virus: One Pill Is Enough for All Genotype	*Ki Tae Yoon, Pusan National Univ.*
15:10-15:30	Hepatitis B Virus: Changing Antiviral Treatment Strategies: Low Viral Load in Liver Cirrhosis with Hepatitis B Virus	*Dong Hyun Sinn, Sungkyunkwan Univ.*
15:30-16:30	Coffee Break & Poster Oral Presentation	
16:30-18:10	**Special Interest Group Symposium 1** Nonalcoholic Fatty Liver Disease (NAFLD): Non-obese NAFLD Patients	*Kwon Yoo (Ewha Womans Univ.), So-Young Jin (Soonchunhyang Univ.)*
16:30-16:50	Difference between Western and Eastern NAFLD Patients	*Eiji Miyoshi, Osaka Univ.*
16:50-17:10	Clinical Differences between Obese and Non-obese NAFLD Patients	*Sang Hoon Park, Hallym Univ.*
17:10-17:30	Genetic Aspect of Non-obese NAFLD Patients	*Luca Valenti, Universita degli Studi di Milano*
17:30-17:50	Therapeutic Approach in Non-obese NAFLD Patients	*Jin-Woo Lee, Inha Univ.*
17:50-18:10	Hepatic Lipid and Glucose Metabolism in NAFLD	*Douglas Mashek, Univ. of Minnesota*

WEST TOWER — Room C [B1]

13:10-14:40	**Health Policy Forum.** Alcoholic Liver Diseases in Korea: Current Status and Multidisciplinary Approach for Effective Management (*K)	*Dong Joon Kim (Hallym Univ.), Moon Seok Choi (Sungkyunkwan Univ.)*
13:10-13:25	Clinician's Perspective on Current Status and Emerging Strategies for Management in Alcoholic Liver Diseases	*Dong Joon Kim, Hallym Univ.*
13:25-13:40	Journalist's Perspective on Current Status and Emerging Strategies for Management in Alcoholic Liver Diseases	*Jin Han Lee, The Dong-A Ilbo*
13:40-13:55	Jurist's Perspective on Current Status and Emerging Strategies for Management in Alcoholic Liver Diseases	*Soon Hyuk Son, Daegu High Prosecutors' Office*
13:55-14:10	Public Health Politician's Perspective on Current Status and Emerging Strategies for Management in Alcohol-related Health Problem	*Jeon Kyung Cha, Ministry of Health and Welfare*
14:10-14:40	Panel Discussion	

EAST TOWER — Room A [2F]

08:30-09:50	**KLTS Symposium 1** How to Minimize Living Donor's Damage and Maximize Living Donor's Safety? [*K] *Hee Jung Wang (Ajou Univ.), Soon Il Kim (Yonsei Univ.)*	
08:30-08:50	Intra-operative Management for Donor Safety during Laparoscopic Donor Hepatectomy	*Choon Hyuck David Kwon, Sungkyunkwan Univ.*
08:50-09:10	Early Experience of Robotic Donor Hepatectomy: Learn from Pioneer	*Gi Hong Choi, Yonsei Univ.*
09:10-09:30	Post-donated Complications after Donor Hepatectomy: Achilles Heel of Donor Surgeon	*Young Seok Han, Kyungpook National univ.*
09:30-09:50	Fate of Live Donor after Liver Donation: Physician's View	*Dong Hyun Sinn, Sungkyunkwan Univ.*
09:50-10:10	Coffee Break	
10:10-12:10	**KLTS Symposium 2** How Far Extended Criteria for Advanced Hepatocellular Carcinoma in Liver Transplantation? [*K] *Joo-Seop Kim (Hallym Univ.), Hee Chul Yu (Chonbuk National Univ.)*	
10:10-10:34	Is Zero Recurrence Possible?: Predictor of Recurrence after Liver Transplantation for Hepatocellular Carcinoma	*Hae Won Lee, Seoul National Univ.*
10:34-10:58	Acceptable Guidelines of Liver Transplantation for Advanced Hepatocellular Carcinoma	*Chong Woo Chu, Pusan National Univ.*
10:58-11:22	Liver Transplantation for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis	*Jong Man Kim, Sungkyunkwan Univ.*
11:22-11:46	Adjuvant Therapy for Prevention of Recurrence of Hepatocellular Carcinoma after Liver Transplantation	*Jae Min Chun, Kyungpook National Univ.*
11:46-12:10	Multi- and Inter-disciplinary Approach for Recurrent Hepatocellular Carcinoma	*Dong Jin Joo, Yonsei Univ.*
12:10-13:10	Luncheon Symposium 4 [by Dong-A ST]	

EAST TOWER — Room BC [2F]

08:30-09:50	**KASL-KLCA Joint Symposium** Cure of Hepatitis B Virus and Hepatocellular Carcinoma *Mong Cho (Pusan National Univ.), Joong-Won Park (National Cancer Center)*	
08:30-08:50	Hepatocellular Carcinoma: Immune Check Point Blockade	*Andrew X. Zhu, Harvard Univ.*
08:50-09:10	Immune Engineering toward a Cure of Hepatitis B Virus	*Su-Hyung Park, KAIST*
09:10-09:30	New Therapeutic Perspectives for Hepatitis B Virus Cure	*Jia-Horng Kao, National Taiwan Univ.*
09:30-09:50	Predictive Molecular Pathology in Hepatocellular Carcinoma: In the Era of Targeted Therapy	*Ju-Seog Lee, MD Anderson Cancer Center*
09:50-10:10	Coffee Break	
10:10-11:20	**Multidisciplinary Approach to Patients with Transarterial Chemoembolization Failure** *Yun Hwan Kim (Korea Univ.), Seung Woon Paik (Sungkyunkwan Univ.)*	
10:10-10:30	Transarterial Chemoembolization Refractoriness / Failure	*Joong-Won Park, National Cancer Center*
10:30-10:50	Rescue Therapies for Transarterial Chemoembolization Failure and Clinical Outcomes	*Josep M. Llovet, Hospital Clinic of Barcelona*
10:50-11:10	Radiation Therapy as a Potential Modality for Patients with Transcatheter Arterial Chemoembolization Failure	*Mi-Sook Kim, Korea Cancer Center Hospital*
11:10-11:20	Discussion	

EAST TOWER — Room BC [2F]

11:20-12:10	KLCA General Meeting	
12:10-13:10	Luncheon Symposium 5 [by Bayer]	
13:10-15:15	KLCA-KHBPS Joint Symposium [*K]	
	Optimal Management of Recurrent Hepatocellular Carcinoma after Resection	*Kwan Sik Lee (Yonsei Univ.), Kyung-Suk Suh (Seoul National Univ.)*
13:10-13:35	Follow-up Protocol after Resection: Risk-based or Unified	*Shin Hwang, Univ. of Ulsan*
13:35-14:00	Locoregional Therapy for Recurrent Hepatocellular Carcinoma after Resection	*Ji Hoon Kim, Korea Univ.*
14:00-14:25	Re-resection: Indication and Limitation	*Kyung Sik Kim, Yonsei Univ.*
14:25-14:50	Salvage Liver Transplantation: Role and Limitation, Optimal Patient Selection	*Choon Hyuck David Kwon, Sungkyunkwan Univ.*
14:50-15:05	Rebuttal with Case Discussion	*Jeong Heo, Pusan National Univ.*
15:05-15:15	Discussion	
15:15-15:30	Korea Central Cancer Registry [*K]	*Soon Ho Um (President of KLCA)*
	Hepatocellular Carcinoma Random Sample Analysis Report	*Young-Suk Lim, Director of the Liver Cancer Registry Committee of KLCA*
15:30-16:30	Coffee Break & Poster Oral Presentation	
16:30-17:30	Emerging Therapies for Hepatocellular Carcinoma [*K]	*Jae Seok Hwang (Keimyung Univ.), Jung-Hwan Yoon (Seoul National Univ.)*
16:30-16:50	Searching for Biomarker-driven Therapy for Hepatocellular Carcinoma	*Si Hyun Bae, The Catholic Univ. of Korea*
16:50-17:10	Molecular Targeted Therapy for Hepatocellular Carcinoma: Learing from Genome-matched Trials in Other Solid Cancers	*Jeeyun Lee, Sungkyunkwan Univ.*
17:10-17:30	Advances in Percutaneous Ablation Therapies for Hepatocellular Carcinoma	*Won Young Tak, Kyungpook National Univ.*

EAST TOWER — Room D [2F]

07:00-08:00	Early Morning Workshop 1 [*K] [HBV] Unsolved Issues in the Management of Chronic Hepatitis B	
	Young-Suk Lim (Univ. of Ulsan), Hyung Joon Yim (Korea Univ.)	

EAST TOWER — Room E [2F]

07:00-08:00	Early Morning Workshop 2 [HCV] Anti-HCV Treatment for Special Population	
	Maria Buti (Hospital Universitari Vall d'Hebron), Oidov Baatarkhuu (Mongolian National Univ. of Medical Sciences), Chang Wook Kim (The Catholic Univ. of Korea), Geum-Youn Gwak (Sungkyunkwan Univ.)	

WEST TOWER — Room F [2F]

13:10-14:10	KLTS Coordinator Session [*K]	*Hea Seon Ha (Asan Medical Center), Bok Nyeo Kim (Samsung Medical Center)*
13:10-13:25	Preoperative Evaluation of Living Donor Candidate for Liver Transplantation	*Sanghee Song, Seoul National Univ. Hospital*
13:25-13:40	Education and Counselling for Living Donor for Liver Transplantation	*Sunyoung Son, Gangnam Severance Hospital*
13:40-13:55	Preparation for Emergency Liver Transplantation	*Ji Yeon Park, Seoul St. Mary's Hospital*
13:55-14:10	Immuno Suppression after Liver Transplantation	*Jeong Hee Kang, Pusan National Univ. Yangsan Hospital*

Program at a Glance

DAY 3 Saturday, June 18, 2016

■ WEST TOWER ■ EAST TOWER

	ROOM AB	ROOM C	ROOM D	ROOM A	ROOM B	ROOM D	ROOM E
08:00						Breakfast Workshop [by Bayer] (07:00-08:20)	
09:00	Symposium 2 Pros & Cons of LC-Controversial Issues (08:30-09:50)	KHBPS-KLTS Joint Symposium (08:30-09:50)		Symposium 3 Nonalcoholic Fatty Liver Disease (08:30-09:50)			
10:00	Coffee Break (09:50-10:10)						
11:00	Plenary Session 2 (10:10-12:10)						
12:00							
13:00	Luncheon Symposium 6 [by Gilead] (12:10-13:10)	Luncheon Symposium 7 [by Novartis] (12:10-13:10)					
	Special Lecture 2 (13:10-13:40)	KHBPS-JSHBPS Joint Symposium 1 (13:10-14:10)					
14:00	Special Interest Group Symposium 2 Cirrhosis with Portal Hypertension (13:50-15:10)		Free Paper 8 HCC, Basic (13:50-15:20)	Free Paper 9 Liver Cirrhosis, HCC and Clinical (13:50-15:20)	Free Paper 10 Basic and Cell Biology (13:50-15:20)		
15:00		KHBPS-JSHBPS Joint Symposium 2 (14:10-15:30)					
16:00	Coffee Break & Poster Oral Presentation (15:30-16:30)						
17:00		Free Paper 11 Surgery (16:30-17:40)	Free Paper 12 Liver Cirrhosis and HCC (16:30-17:40)	Free Paper 13 HCC, Clinical (16:30-17:40)	Free Paper 14 HCC, Clinical (16:30-17:40)		
18:00	Closing & Award Ceremony (17:40-18:00)						

The Korean Association of HBP Surgery (KHBPS) The Korean Liver Transplantation Society (KLTS) Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS)

WEST TOWER — Room AB [B1]

08:30-09:50	Symposium 2 Pros and Cons of LC-Controversial Issues	*Samuel Lee (Univ. of Calgary), Sung Won Cho (Ajou Univ.)*
08:30-08:50	Nonselective Beta Blocker: Hemodynamic Effects vs. Non-hemodynamic Effects	*Moon Young Kim, Yonsei Univ. Wonju*
08:50-09:10	Scoring Systems for Alcoholic Hepatitis	*Patrick S. Kamath, Mayo Clinic*
09:10-09:30	Anticoagulation: Do or Avoid?	*Erica Villa, Univ. of Modena and Reggio Emilia*
09:30-09:50	Albumin: New Roles beyond Volume Expander	*Samuel Lee, Univ. of Calgary*
09:50-10:10	Coffee Break	
10:10-12:10	Plenary Session 2	*2-1. Choong Kee Park (Hallym Univ.), Chang-Min Kim (National Cancer Center)* *2-2. Kwang-Hyub Han (Yonsei Univ.), Kyung-Suk Suh (Seoul National Univ.)*
12:10-13:10	Luncheon Symposium 6 [by Gilead]	
13:10-13:40	Special Lecture 2	*Kwan Soo Byun (Korea Univ.)*
	Hepatitis C Virus: Next Generation of DAAs	*Mark Sulkowski, Johns Hopkins Univ.*
13:50-15:10	Special Interest Group Symposium 2 Cirrhosis with Portal Hypertension: Liver-Heart-Kidney Axis, from Portal Hypertension to Hyperdynamic Circulatory Syndrome	*Joo Hyun Sohn (Hanyang Univ.), Soon Koo Baik (Yonsei Univ. Wonju)*
13:50-14:10	The Diagnosis of Acute Kidney Injury in Cirrhosis: The Reasonable Cut-off Serum Creatinine Value	*Florence Wong, Univ. of Toronto*
14:10-14:30	The Current Management of Acute Kidney Injury in Cirrhosis	*Soung Won Jeong, Soonchunhyang Univ.*
14:30-14:50	Role of Heart in Refractory Ascites, Acute Kidney Injury, and Hepatorenal Syndrome	*Samuel Lee, Univ. of Calgary*
14:50-15:10	The Liver in Cardiac Disease	*Patrick S. Kamath, Mayo Clinic*
15:30-16:30	Coffee Break & Poster Oral Presentation	
17:40-18:00	Closing & Award Ceremony	

WEST TOWER — Room C [B1]

08:30-09:50	KHBPS-KLTS Joint Symposium How Can We Overcome Complicated Portal Vein?	*Dong Goo Kim (The Catholic Univ. of Korea), Jae-Won Joh (Sungkyunkwan Univ.)*
08:30-08:50	Indication or Contraindication of Liver Transplantation in Patient with Portal Vein Thrombosis	*Nam-Joon Yi, Seoul National Univ.*
08:50-09:10	Anatomical Reconstruction	*Gyu-Seong Choi, Sungkyunkwan Univ.*
09:10-09:30	How to Overcome Complicated Portal Vein Thrombosis? Extra-anatomic Bypass	*Deok-Bog Moon, Univ. of Ulsan*
09:30-09:50	Intervention for Complicated Portal Vein	*Gi-Young Ko, Univ. of Ulsan*
09:50-10:10	Coffee Break	
12:10-13:10	Luncheon Symposium 7 [by Novartis]	

WEST TOWER

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13:10-13:30	Primary Liver Cancer Registry in Japan: How Has It Been Evolving?	*Norihiro Kokudo, The Univ. of Tokyo*
13:30-13:50	Random Sampling of Korea Central Cancer Registry for Hepatocellular Carcinoma	*Young-Suk Lim, Univ. of Ulsan*
13:50-14:10	What and How to Build Up Solid Evidences for Surgical Treatment of Hepatocellular Carcinoma	*Choon Hyuck David Kwon, Sungkyunkwan Univ.*
14:10-15:30	KHBPS-JSHBPS Joint Symposium 2 Incorporating Recent Technologies in Liver Surgery	*Atsushi Sugioka (Fujita Health Univ.), Dong-Sup Yoon (Yonsei Univ.)*
14:10-14:30	Laparoscopic and Robotic Liver Resection Using Advanced 3D Liver Simulation Software	*Atsushi Sugioka, Fujita Health Univ.*
14:30-14:50	Laparoscopic Liver Resection Using 3D Camera System	*Kyung-Suk Suh, Seoul National Univ.*
14:50-15:10	Application of Indocyanine Green Fluorescence Imaging in Liver Resection	*Norihiro Kokudo, The Univ. of Tokyo*
15:10-15:30	Liver Resection Using Robotic System	*Gi Hong Choi, Yonsei Univ.*
15:30-16:30	Coffee Break & Poster Oral Presentation	

EAST TOWER

Room AB [2F]

08:30-09:50	Symposium 3 Nonalcoholic Fatty Liver Disease	*Joung-Il Lee (Kyung Hee Univ.), Seung Kew Yoon (The Catholic Univ. of Korea)*
08:30-08:50	Lipid Droplet as a Potential Target for Nonalcoholic Fatty Liver Disease	*Douglas Mashek, Univ. of Minnesota*
08:50-09:10	Noninvasive Diagnositic Method of Nonalcoholic Steatohepatitis	*Eiji Miyoshi, Osaka Univ.*
09:10-09:30	Hepatocellular Carcinoma Development in Nonalcoholic Fatty Liver Disease	*Luca Valenti, Universita degli Studi di Milano*
09:30-09:50	Molecular Targets for Nonalcoholic Steatohepatitis Therapeutics	*Yong Kyun Cho, Sungkyunkwan Univ.*

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07:00-08:20	Breakfast Workshop [by Bayer]

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7. Liver Transplantation

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9. Liver Cirrhosis, HCC and Clinical

10. Basic, Cell Biology

13. HCC, Clinical

14. HCC, Clinical

Poster Oral Presentation

Cell Biology and Basic

HCV, Clinical

Liver Cirrhosis

NAFLD

Liver Cirrhosis and Others

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HBV, Clinical

HBV, Clinical

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HCC, Basic

HCC, Clinical

HCC, Clinical

HCC, Clinical

7. HCV, Clinical

12. Liver Failure, Acute

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14. Liver, Infectious Disease

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Symposium 2 Pros and Cons of LC-Controversial Issues

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DAY 2: JUNE 17, 2016 (FRI) (10:10-12:10)

Plenary Session 1

Chairs : **PART 1**
W. Ray Kim (Stanford Univ.)
Soon Ho Um (Korea Univ.)

PART 2
Byung Chul Yoo (Konkuk Univ.)
Jae-Won Joh (Sungkyunkwan Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

PS 1-1

Virus-induced IFN-λ4 Potently Blocks IFN-α Signaling by ISG15/USP18 in HCV Infection : Implication for Increased IFN Responsiveness after DAA Treatment

Pil Soo Sung[1,3], Seon-Hui Hong[1], Su-Hyung Park[2], Eui-Cheol Shin[1]

[1]Laboratory of Immunology and Infectious Diseases, Graduate School of Medical Science and Engineering, KAIST, Daejeon 34141, Korea, [2]Laboratory of Translational Immunology and Vaccinology, Graduate School of Medical Science and Engineering, KAIST, Daejeon 34141, Korea, [3]Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

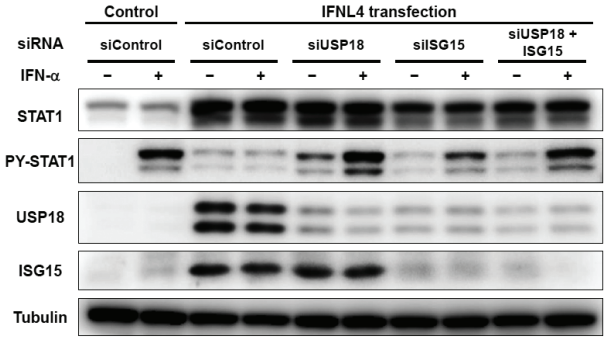
Aims: IFN-λ4 is a newly identified type III IFN, and its genetic polymorphism has been proven to predict responses to IFN-α-based therapy in hepatitis C virus (HCV)-infected patients. The IFNL4-TT genotype, which does not produce IFN-λ4 protein due to a premature stop codon, is associated with a favorable treatment response while the IFNL4-DG genotype coding for functional IFN-λ4 protein is associated with a poor treatment response. Recently, we demonstrated that prolonged exposure to IFNs results in IFN-α unresponsiveness by ISG15 induction and USP18 stabilization (Sung et al. PNAS 2015). In the present study, we studied the induction of IFN-λ4 in HCV-infected hepatocytes and investigated the biological effects of IFN-λ4 in relation to IFN responsiveness. Furthermore, we studied the effects of DAA treatment on the induction of IFN-λ4 and IFN responsiveness.

Methods: Primary human hepatocytes (PHHs) were infected with JFH1 HCVcc at high titer. Hepatoma cells were transfected with IFNL4-encoding plasmid various experiments were performed to identify the biological effects of IFN-λ4.

Results: JFH1 HCVcc infection induced IFN-λ4 gene expression in PHHs. After IFNL4 gene transfection in hepatoma cells, IFN-λ4 protein was scarcely detected in culture supernatant as previously reported. However, IFN-λ4 robustly increased the protein levels of ISG15 and USP18 in an IFNLR-dependent manner and potently reduced IFN-α responsiveness. The ISG15/USP18-mediated IFN-α unresponsiveness was confirmed by transfection of siRNAs for ISG15 and/or USP18. This potent activity of IFN-λ4 was related with unphosphorylated ISGF3, formed by high levels of IRF-9, STAT-1 and STAT-2. Telaprevir treatment to HCV-infected PHHs decreased the induction of IFN-λs including IFN-λ4 and restored the IFN responsiveness.

Conclusions: The current data demonstrate that virus-induced IFN-λ4 potently induces ISG15/USP18-mediated IFN- α unresponsiveness. Our data clearly demonstrate that HCV-infected hepatocytes restore IFN responsiveness after DAA therapy.

Keywords: IFN-λ4, Hepatitis C virus, USP18, DAA



PS 1-2

Sofosbuvir/Velpatasvir (SOF/VEL) for 12 Weeks in Genotype 1, 2, 4, 5, 6 HCV Patients: Results of the ASTRAL-1 Study

Mark S. Sulkowski[1], Henry Lik Yuen Chan[2], Jordan J. Feld[3], Kosh Agarwal[4], Christophe Hezode[5], Tarik Asselah[6], Peter J. Ruane[7], Norbert Gruener[8], Armand Abergel[9], Alessandra Mangia[10], Ching-Lung Lai[11], Francesco Mazzotta[12], Christophe Moreno[13], Eric Yoshida[14], Stephen D. Shafran[15], William J. Towner[16], Tram T. Tran[17], Yanni Zhu[18], Evguenia Svarovskaia[18], John McNally[18], Anu Osinusi[18], Macky Natha[18], Diana M Brainard[18], John G McHutchison[18], Ira M. Jacobson[19], Stefan Zeuzem[20]

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Background: Velpatasvir (VEL) is a pangenotypic HCV-NS5A inhibitor. This Phase 3 study evaluated treatment with a fixed dose combination of SOF/VEL for 12 weeks in patients with genotype 1, 2, 4, 5, or 6 HCV infection.

Methods: Patients with genotype 1, 2, 4, or 6 chronic HCV infection were randomized 5:1 to received SOF/VEL (400 mg /100 mg daily) or placebo for 12 weeks. Patients with genotype 5 infection were enrolled to the SOF/VEL treatment group and patients with genotype 3 were evaluated in a separate study.

Results: 740 patients were enrolled at 81 international sites: 60% male, 79% white, 32% treatment-experienced (TE), and 19% compensated-cirrhosis. Of the 624 patients treated with SOF/VEL, the genotype distribution was 53% GT1, 17% GT2, 19% GT4, 6% GT5 and 7 % GT6. Overall SVR12 for SOF/VEL-treated patients was 99.0% and the study met its primary efficacy endpoint. SVR12 rates by HCV genotype are presented in the table. Two of 328 patients (0.6%) with genotype-1 infection had virologic relapse. No patients with genotype 2, 4, 5, or 6, including 48 with cirrhosis, had virologic failure. Four patients did not achieve SVR12 for non-virologic reasons. AEs and laboratory abnormalities were similar in the SOF/VEL-treated

patients compared with the 116 placebo-treated patients. One patient discontinued SOF/VEL treatment due to adverse-events.

Conclusions: Treatment with the once daily, all-oral, single tablet regimen of SOF/VEL for 12 weeks is well tolerated and results in high SVR12 rates in treatment-naïve and treatment-experienced genotype 1, 2, 4, 5, and 6 HCV-infected patients with and without cirrhosis.

HCV Genotype	Total (N=624)	GT 1 (N=328)	GT 2 (N=104)	GT 4 (N=116)	GT 5 (N=35)	GT 6 (N=41)
Cirrhosis %, (n/N)	19.4% (121/624)	22.3% (73/328)	9.6% (10/104)	23.3% (27/116)	14.3% (5/35)	14.6% (6/41)
SVR12 %, (n/N)	99.0% (618/624)	98.5% (323/328)	100.0% (104/104)	100.0% (116/116)	97.1% (34/35)	100.0% (41/41)

Keywords: Sofosbuvir, Velpatasvir, Phase 3, ASTRAL-1

PS 1-3

Daclatasvir Plus Sofosbuvir ± Ribavirin for Treating Chronic HCV Infection in Patients with Advanced Liver Disease: European Compassionate Use Program Results

Sandzhar Abdullaev[14], T.M. Welzel[1], J. Petersen[2], K. Herzer[3], P. Ferenci[4], M. Gschwantler[5], M. Cornberg[6], P. Ingiliz[7], T. Berg[8], U. Spengler[9], O. Weiland[10], M. van der Valk[11], H. Klinker[12], J. Rockstroh[9], M. Peck-Radosavljevic[13], Y. Zhao[14], M.J. Jimenez-Exposito[14], S. Zeuzem[1]

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Aims: The all-oral, pan-genotypic combination of daclatasvir+sofosbuvir±ribavirin (DCV+SOF±RBV) demonstrated high sustained virologic response rates at posttreatment Week 12 (SVR12) in phase 3 studies of patients with chronic HCV. We report efficacy and safety results from a large European compassionate use program that provided DCV+SOF±RBV therapy to patients with chronic HCV infection and severe liver disease.

Methods: Eligible patients were adults with chronic HCV infection at a high risk of hepatic decompensation or death within 12 months if left untreated, or urgent need of viral clearance due to extrahepatic manifestations or comorbidities, and with no available treatment options. Patients received DCV(60mg)+SOF(400mg) once daily for 24 weeks; RBV addition or reduced treatment duration was the physician's choice. The primary efficacy outcome was SVR12.

Results: Efficacy data were available for 436/485 patients enrolled. Most patients were HCV treatment experienced (70%) with mean HCV RNA 5.5 log10 IU/mL. 388 (80%) patients had confirmed cirrhosis(Child-Pugh class B or C, 165 (43%); MELD scores>15, 37 (10%)) , 87 patients (18%) had received liver transplants and 55 (11%) were HIV/HCV coinfected. SVR12 was achieved by 394/436 (90%) patients (table). There were 13 relapses and 1 on-treatment virologic failure. SVR12 rates were similar with/without ribavirin and comparable across HCV GT, presence of cirrhosis, liver transplant status, HIV coinfection,

SVR12, n/N (%) [a]	DCV+SOF (N=359)	DCV+SOF+RBV (N=126)	Total
Overall	297/326 (91)	97/110 (88)	394/436 (90)
GT 1a	116/121 (96)	25/26 (96)	141/147 (96)
GT 1b	115/130 (88)	31/35 (89)	146/165 (88)
GT 3	42/49 (86)	29/33 (88)	71/82 (87)
GT 4	12/12 (100)	6/6 (100)	18/18 (100)
With cirrhosis	233/258 (90)	78/90 (87)	311/348 (89)
HIV/HCV coinfected	31/34 (91)	14/15 (93)	45/49 (92)
Liver transplant recipients	54/58 (93)	20/22 (91)	74/80 (93)

[a] HCV RNA below lower limit of quantification, target detected or target not detected (modified intention-to-treat analysis)

and other baseline characteristics. There were 28 deaths over treatment or follow-up (none considered treatment-related), 91 experienced serious adverse events (11 considered treatment-related), and 38 discontinued treatment or died due to adverse events (10 treatment-related). Most deaths and serious adverse events were directly or indirectly associated with advanced liver disease. Adverse events (any grade) occurring in ≥5% of patients were fatigue, anaemia, headache, nausea, and diarrhoea.

Conclusions: The all-oral regimen of DCV+SOF±RBV was highly effective and well tolerated in this large European real-world cohort of patients with advanced liver disease.

Keywords: Chronic HCV, Daclatasvir, Sofosbuvir, Advanced Liver Disease

PS 1-4

Prospective Comparison between TE, SSI, and ARFI for Predicting Fibrosis in Subjects with NAFLD

Won Kim[1], Myoung Seok Lee[2], Jung Ho Kim[3]

[1]Department of Internal medicine, Seoul National University College of Medicine, Seoul Metropolitan Government Boramae Medical Center, [2]Department of Radiology, Seoul National University College of Medicine, Seoul Metropolitan Government Boramae Medical Center, [3]Department of Pathology, Seoul National University College of Medicine, Seoul Metropolitan Government Boramae Medical Center

Aims: To compare the diagnostic performance of transient elastography (TE), supersonic shear-wave imaging (SSI), and acoustic radiation force impulse (ARFI) imaging for staging liver fibrosis and to find clinical factors which affect liver stiffness measurement (LSM) in a prospective NAFLD cohort.

Methods: Ninety-four patients with histologically confirmed NAFLD were included in this prospective cohort study. For each patient, liver stiffness was measured using TE, SSI, and ARFI within 1 month of percutaneous liver biopsy. Diagnostic performance for staging liver fibrosis was evaluated using receiver operating characteristic (ROC) analysis. Clinical, laboratory, and anthropometric data using fat-amount CT and bioelectrical impedance analysis were evaluated as covariates influencing LSM by regression analyses.

Results: All three LSM methods were well correlated with fibrosis stages (NASH CRN) (r= 0.416~0.532, p<0.001) and exhibited statistically similar diagnostic performance for staging fibrosis; the area under the receiver operating characteristic (AUROC) curves for TE (kPa), SSI (m/s), SSI (kPa), and ARFI (m/s) were 0.757, 0.761, 0.759, and 0.657 for diagnosing ≥F2, 0.870, 0.816, 0.809, and 0.873 for ≥F3, and 0.882, 0.900, 0.906, and 0.920 for F4, respectively (p>0.05). ARFI tended to be more specific and SSI tended to be more sensitive

to differentiate each fibrosis stage with their best diagnostic performances showing the highest Youden's index. Anthropometric data were correlated with failure or unreliability of LSM, especially for SSI LSM. In regression analysis, anthropometric data might be confounding factors for SSI LSM, while serum liver injury-related markers might be confounding factors for TE and ARFI LSM.

Conclusions: Diagnostic performances of individual LSM modalities for staging liver fibrosis in NAFLD patients were not statistically significantly different. TE or ARFI might fit better for suspicion of advanced fibrosis (≥F3) in NAFLD, while TE or SSI could be more advantageous for suspicion of mild fibrosis (F0~F2) in NAFLD. Pre-LSM anthropometric evaluation may help predicting LSM reliability, especially for SSI.

Keywords: Steatosis, Fibrosis, Shear wave velocity, Elastography

PS 1-5

The Functional Impact of HBV Integration into the Telomerase Reverse Transcriptase Promoter on Hepatocarcinogenesis

Jeong Won Jang[1,2], Abdul M. Oseini[2], Ying Li[2], Catherine D. Moser[2], Karl J. Clark[2], Lewis R. Roberts[*2]

[1]Departments of Internal Medicine, The Catholic University of Korea, College of Medicine, Korea, [2]Division of Gastroenterology and Hepatology, Mayo Clinic Cancer Center, Rochester, MN, USA

Aims: HBV integration into the cellular genome is frequently found in HCC and associated with genomic instability, leading to hepatocarcinogenesis. Telomerase-reverse transcriptase (TERT) promoter mutation was recently suggested to be gatekeeper in HCC. Interestingly, recent high-throughput DNA sequencing studies demonstrate that HBV integration is not random, with the highest frequency in telomere-related genes. The study aimed to investigate the molecular effect of HBV integration into the TERT promoter on hepatocarcinogenesis.

Methods: Sixteen hepatoma/normal cell lines were sequenced for hTERT promoter mutation, followed by real-time RT-PCR for hTERT expression. Integration plasmid, pKT2C-HBx-TERTpmt-Luc containing HBx integrated into the various sites on hTERT promoter, was constructed and transfected into the cells. To generate genomic rearrangements associated with integration, HBx C-terminal truncation (aa27) and then hTERT hot spot mutation (-124C>T) were introduced in the HBx-hTERT fusion fragment by site-directed mutagenesis. The molecular functions of the HBx-hTERT integrants were examained by luciferase reporter and cell proliferation/apoptosis assays.

Results: hTERT promoter mutation was detected in 7 (43.8%) of 16 cell lines. HCC cells with both HBV integration and hTERT promoter mutation showed a higher hTERT mRNA expression than those with either one alone or none. Although full-length HBx integration (Fl-HBx-TERT) exerts no or rather repressive effect on hTERT transcription, insertion of C-terminally truncated HBx (Tr-HBx-TERT) restored cis-activation of hTERT. The strongest effect was observed with further generation of hTERT promoter mutation (Tr-HBx-mt-TERT). Consistently, the HBx-hTERT integrants induced cell proliferation and inhibited apoptosis (caspases 3/7-dependent), with a general trend toward increasing effect from Fl-HBx-TERT to Tr-HBx-TERT and to Tr-HBx-mt-TERT.

Conclusions: HBV integration can regulate the transcriptional activity of hTERT in cis and increase cell proliferation through anti-apoptotic actions, with a stronger oncogenic effect when HBx-truncation and hTERT promoter mutation are associated with integration. These findings provide insight into the implications of genomic rearrangements occurring at the viral-host junctions in integration-mediated hepatocarcinogenesis.

Keywords: Hepatitis B virus, Virus integration, Telomerase, Genomic Instability, Hepatocellular carcinoma

PS 1-6

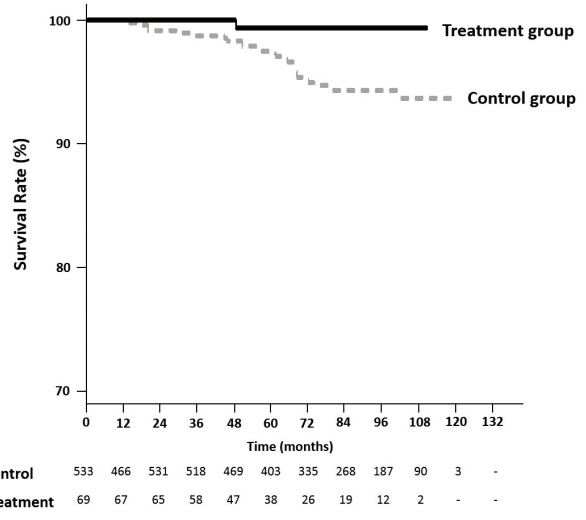
Nucleos(t)ide Analogue Treatment for Chronic Hepatitis B Patients in Highly Replicative but Immune-tolerant or Mild Inflammatory Phase Prolongs Overall Survival

Young Chang[1], Won Hyeok Choe[2], Dong Hyun Sinn[3], Jeong-Hoon Lee[1*], Joon Yeul Nam[1], Hyeki Cho[1], Young Youn Cho[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]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea, [3]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: The antiviral treatment for chronic hepatitis B (CHB) patients in highly replicative but low inflammatory phase (including immune tolerant phase) is still controversial. The aim of this study is to assess whether antiviral treatment can improve survival in HBeAg-positive CHB patients with high HBV DNA but normal to mildly elevated ALT level.

Methods: This multi-center retrospective study included 602 patients diagnosed as HBeAg-positive CHB with HBV DNA above 20,000 IU/mL and ALT below 80 IU/L without evidence of liver cirrhosis (LC) in three large volume medical centers in Korea. The involved patients were categorized into two groups; antiviral treatment group (n=69) and control group (n=533). Primary endpoint was overall survival (OS) and secondary endpoints were development of LC and hep-



atocellular carcinoma (HCC). To compare the endpoints, baseline characteristics of the two groups were adjusted or balanced by Cox proportional hazards model and inverse probability weighting (IPW).

Results: Baseline liver function was more favorable for the control group. In multivariate analysis, the treatment group showed significantly lower risk of developing LC (adjusted hazard ratio [aHR]=0.326; P=0.006) and HCC (aHR=0.202; P=0.016), and consequently longer OS (aHR=0.137; P=0.052) than the control group. After balancing the baseline characteristics between the two groups by IPW, antiviral treatment significantly prolonged OS (aHR=0.067; P=0.016) (Figure 1) and the risk of LC (aHR=0.169; P<0.001) and HCC (aHR=0.101; P<0.001) in the treatment group were also reduced significantly compared to the control group. Assuming to treat the relevant patients with entecavir, the additional costs for reducing one patient of LC, HCC, and death were supposed to be approximately 10,000 USD, 25,000 USD, and 45,000 USD, respectively, in Korea.

Conclusions: Antiviral therapy for CHB patients with high viral load prolongs OS and reduces the risk of LC and HCC even if ALT levels would not exceed two times of upper limit of normal.

Keywords: Chronic hepatitis B, Immune tolerant phase, Survival, Hepatocellular carcinoma

PS 1-7

Recent Advancements in the Pediatric Liver Transplantation : A Single-center Study of 235 Patients Over 27 Years

Sung-Woo Ahn, Nam-Joon Yi*, Kyung Chul Yoon, Suk Kyun Hong, Hyo-Sin Kim, Hyeyoung Kim, Youngrok Choi, Kwang-Woong Lee, Kyung-Suk Suh

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

Purpose: Pediatric liver transplantation (PLT) has been the key therapy for end stage liver disease and the outcome has been excellent. However, still surgical complication associated with small recipient is the main cause of graft loss. In the present study, we assessed recent advances in outcome of PLTs through our experience.

Methods: A total of 235 PLTs performed between Mar 1988 and July 2015 were analyzed. Three chronological periods were investigated: the initial period (1988-2007, n=117), the mid-term period in which our PLT management protocol was settled down (2008-2011, n=62), and the period in which surgical procedures were refined for small children (2012-2015, n=56).

Results: The grafts' (84% vs. 82% vs. 98%) and patients' (84% vs. 87% vs. 98%) survival have been improved (p<0.05), whereas the number of biliary atresia (31% vs. 45% vs. 50%) deceased and the proportion of deceased donor (24% vs. 36% vs. 52%) and split PLT (7%vs. 16% vs. 46%) increased (p<0.05). The number of re-LT (3% vs. 9% vs. 2%) has been changed. ABO incompatible PLT has introduced on the last period (9%).

Conclusion: The quality of the PLT has recently been standardized through a large volume of experience, and the operation has been proven to improve the survival outcome. However, a constant evaluation of our experience is critical for further progress.

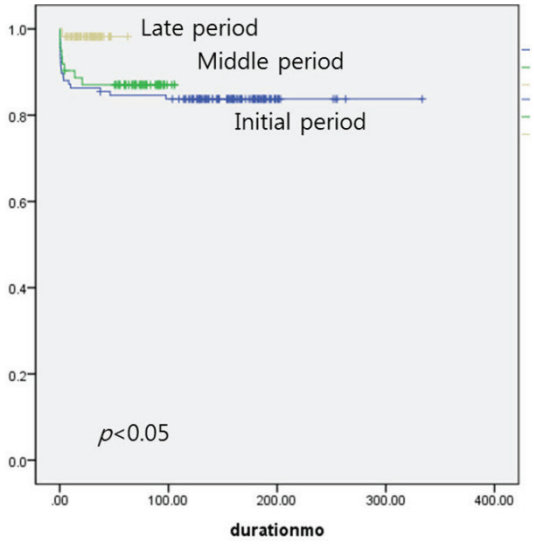


Figure 1. Kaplan-Meier survival estimates

PS 1-8

A Clinical Trial to Evaluate the Pharmacokinetic Characteristics of Hepatitis B Immunoglobulin Used for Prevention of Hepatitis B Recurrence after Liver Transplantation

Gun Hyung Na[1], Seunghoon Han[2], Sung Ho Choi[1], Tae Ho Hong[1], Young Kyoung You[1], Dong Goo Kim[1*]

Department of [1]Surgery, [2]Pharmacology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Korea

Purpose: Hepatitis B virus (HBV) is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in Asia and is responsible for approximately 500,000 deaths per year worldwide. The HBV recurrence rate after LT is greater than 80% without any prophylaxis, and HBV reinfection may lead to rapid disease progression and early graft loss. Prevention of HBV recurrence after LT is essential in HBV-related patients. In recent years, the combination of long-term hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues is currently the standard treatment and has effectively reduced HBV recurrence rates. However, there are few studies about the pharmacokinetic characteristics of HBIG. In the present study, we assessed the pharmacokinetic characteristics of HBIG, clinical factors influencing the concentration of HBIG, and the appropriate dose of HBIG.

Methods: HBsAg-Positive adult HBV patients who were scheduled to receive liver transplantation followed by preventive immunoglobulin treatment were eligible to the study. All patients were treated with a combination of HBIG and nucleos(t)ide analogues for prophylaxis of HBV recurrence, and were given 10,000 units of HBIG intravenously during the anhepatic phase, which was followed daily for 7 days and then every month for 6 months after LDLT. Whole blood samples were obtained at 30 minutes after the first administration and at predose and 1 hour after the dose of day 1, 7, 28, 84, 128 for pharmacokinetic analysis. Mixed-effect modeling was performed using NONMEM (Ver.7.3, Icon Development Solution, Ellicott City, MD).

Results: A total of 228 plasma concentration data were obtained from 20 patients. A 1-compartment model was chosen to explain the dis-

position of immunoglobulin. The overall concentration in the immediate period after transplantation was affected by the level of viral DNA titer and it was included in the model as a covariate for bioavailability under the assumption that the virus is neutralized immediately after the immunoglobulin dosing. The clearance was highest during the 1 week after transplantation and decreased thereafter. The pre-operative clinical factor influencing the concentration of HBIG at day 7 after LT was the level of bilirubin. Currently, the recommended dose for maintenance of immunoglobulin >300 IU/mL is considered to be 3600 IU/month.

Conclusion: Pre-operative the level of viral DNA titer and HBeAg are the most influencing virological factors on the concentration of HBIG in the immediate period after LT. The level of bilirubin is the most influencing clinical factors on the concentration of HBIG in the immediate period after LT. The recommended dose for maintenance of immunoglobulin>300 IU/mL is considered to be 3600 IU/month.

DAY 3: JUNE 18, 2016 (SAT) (10:10-12:10)

Plenary Session 2

Chairs : **PART 1**
Choong Kee Park (Hallym Univ.)
Chang-Min Kim (National Cancer Center)

PART 2
Kwang-Hyub Han (Yonsei Univ.)
Kyung-Suk Suh (Seoul National Univ.)

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PS 2-1

A Phase 3 Study of Tenofovir Alafenamide Compared with Tenofovir Disoproxil Fumarate in Patients with HBeAg-negative, Chronic Hepatitis B

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Aims: Tenofovir alafenamide (TAF), a novel prodrug of tenofovir (TFV), is more stable in plasma and enhances delivery of TFV into hepatocytes while lowering circulating levels of TFV by approximately 90% compared to tenofovir disoproxil fumarate (TDF).

Methods: In this Phase 3 study, patients with HBeAg-negative chronic hepatitis B (CHB) were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD and treated for 96 weeks. After Week 96, patients receive open label TAF for 48 weeks. The primary efficacy analysis was the percent of patients with HBV DNA <29 IU/mL at Week 48. Key secondary safety endpoints were assessed sequentially: changes in hip and spine bone mineral density (BMD), changes in serum creatinine (sCr), and dipstick proteinuria. Markers of bone formation and resorption, and renal tubular function were also assessed.

Results: 425 patients were randomized and treated at 105 sites in 17 countries. Baseline characteristics included: mean age 46 years, 61% males, 72% Asians; 19% had HBV DNA ≥ 7 log10 IU/mL, and 21% were previously treated with nucleos(t)ides. At Week 48, TAF was non-inferior in efficacy to TDF with virologic response of 94.0% with TAF and 92.9% with TDF. A greater percentage of patients treated with TAF also achieved normalization of serum ALT values. Patients on TAF experienced significantly less declines in hip and spine BMD than TDF. No differences were seen in sCr change and proteinuria; however, smaller declines in eGFRCG and smaller changes in renal tubular markers were observed in the TAF arm. No viral resistance was observed in the 4 patients (2 per group) who qualified for testing.

Conclusions: Compared to TDF 300 mg, the efficacy of TAF 25 mg in patients with HBeAg-negative CHB was noninferior. Safety was also improved, with less change in bone and renal parameters.

Keywords: Tenofovir Alafenamide, Tenofovir disoproxil fumarate, HBeAg-negative, Phase 3

Table. Efficacy and Safety at Week 48

n/N (%)	TAF (N=285)	TDF (N=140)	P value
HBV DNA <29 IU/mL	268/285 (94)	130/140 (92.9)	0.47
ALTnormalization (centrallaboratory)[a]	196/236 (83.1)	91/121 (75.2)	0.076
ALT normalization (AASLD criteria)[b]	137/276 (49.6)	44/138 (31.9)	<0.001
Hip BMD, mean (SD) % change (g/cm^2)	-0.29 (2.14)	-2.16 (2.17)	<0.001
Spine BMD, mean (SD) % change (g/cm^2)	-0.88 (2.86)	-2.51 (3.36)	<0.001
sCr, mean (SD) change (mg/dL)[c]	0.01 (0.09)	0.02 (0.10)	0.32
Proteinuria (dipstick)	54/282 (19.2)	26/140 (18.5)	0.90
eGFRCG mean (SD) change (mL/min)[d]	-1.4 (12.7)	-4.7 (12.0)	0.004

Efficacy results are missing = failure;
[a]ULN43U/Lmales,34U/Lfemales;
[b]ULN30U/Lmales,19U/Lfemales;
[c]sCr is serum creatinine; [d]eGFRCGisCLCr(Cockcroft-Gaultmethod)

PS 2-2

Entecavir versus Lamivudine for Prevention of Liver-related Events in Patients with HBV-related Advanced Liver Disease: A Multicenter, Prospective Study

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Aims: High potent drug is being recommended as first-line agent for chronic hepatitis B. However, whether high potent drug reduce the risk of liver- related events (LREs) to a greater extent than lamivudine is known, especially in patients with advanced fibrosis. We

aimed to compare the clinical benefits of entecavir (ETV) 0.5mg versus lamivudine (LAM) 100mg for prevention of LREs in patients with HBV-related advanced liver disease.

Methods: Randomized, open-label, phase 4 study conducted from December 2008 through April 2015 at 18 medical centers in South Korea. Patients who had histologically confirmed advanced fibrosis or cirrhosis or clinically evidence of overt cirrhosis with a high viral loads (HBV DNA≥2,000 IU/mL) and normal or slightly elevated transaminase and no prior antiviral therapy were assigned to receive ETV (n = 231) or LAM (n = 231) for 5 years. If the patients confirmed to have HBV-resistance mutations, adefovir or tenofovir-based rescue therapy was added. LREs included hepatocellular carcinoma (HCC), decompensation, or liver-related death or transplantation.

Results: The baseline characteristics were comparable between these two groups. During the study period, 100 (21.6%) patients experienced LREs (ETV vs LAM: 50 vs 50). The rates were no difference for the ETV group vs the LAM group for HCC development (14.3% vs 14.7%, respectively), Child-Pugh score increase (3.9% vs 3.9%), variceal bleeding (2.6% vs 1.3%) and liver-related death or transplantation (0.9% vs 2.6%). The cumulative incidence rates of genotypic resistance to LAM and ETV at 5-year treatment was 49.8% and 1.2%, respectively. Multivariable analyses showed that age, male gender and a primary nonresponse to antiviral therapy were associated with a high likelihood of a development of LREs, irrespective of the type of antiviral agent.

Conclusions: In this prospective long-term study, there was no difference between the ETV arm and the LAM arm for prevention of LREs in patients with HBV-related advanced liver disease, if applied the appropriate rescue therapy.

Keywords: Entecavir, Lamivudine, Liver-related event, Advanced liver disease

PS 2-3

Risk of Overestimation of Renal Function Using Estimated GFR in Patients with Liver Cirrhosis

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Aims: In the clinical context of the patients with liver cirrhosis, accurate evaluation of the renal function is potentially crucial. Serum creatinine (SCr) is widely used to estimate glomerular fitration rate (GFR), but discrepancy between measured GFR (mGFR) and estimated GFR (eGFR) in cirrhotic patients has not been evaluated yet. In this study, we compared performance of two common eGFR formula compared with mGFR, and evaluated factors associated with overestimation of renal function in cirrhotic patients.

Methods: This retrospective study included consecutive 458 patients who were diagnosed as liver cirrhosis. 51Cr-EDTA was used for assessing actual GFR and eGFR was calculated by two different formulas; i) Modification of Diet and Renal Disease equation (MDRD), ii) CKD-EPI cystatin C equation. eGFR increase by more than 10% of mGFR in each patient was defined as overestimation of GFR. Sarcopenia was defined as an L3 skeletal muscle index of ≤38.5cm2/m2 for women and ≤52.4 cm2/m2 for men using computed tomography. Logistic regression was used to evaluate factors associated with overestimation of renal function.

Results: Mean age of the patients was 53.6±11.5 years and 76.6% were male. Mean SCr was 1.1±0.9mg/dL, and the mean eGFR was 81.8±25.8ml/min by MDRD and 87.3±29.9ml/min by cystatin C. The mean mGFR was 76.0±26.6ml/min, which was significantly lower than eGFR. Cystatin C-eGFR showed better correlation and performance with mGFR compared with MDRD-eGFR (R 0.58 vs. R 0.48). MDRD-eGFR overestimated mGFR among 47% of the patients with liver cirrhosis. A multivariate analysis showed that male gender (hazard ratio [HR] 1.63, 95% confidence interval [CI] 1.03-2.56; P=0.04) and Child-Pugh class (HR 3.3, 95% CI 1.89-5.80; P<0.001) were independent risk factors associated with overestimation of renal function, but not associated with sarcopenia (HR 1.1, 95% CI 0.56-2.36; P=0.09).

Conclusions: In patients with cirrhosis, overestimation of the GFR is common when using SCr and creatinine clearance. Isotopic measurement of GFR or eGFR by cystatin C rather than SCr can be more useful when greater accuracy is required, especially in patients with impaired liver function or male gender.

Keywords: Liver cirrhosis, GFR, Overestimation

PS 2-4

New Paper Pencil Test for the Diagnosis of Minimal Hepatic Encephalopathy in Liver Cirrhosis Patients in Korea

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Aims: Korean association for the study of the liver and Working Party recommends that the diagnosis of minimal hepatic encephalopathy (MHE) requires at least two of the following tests: Number connection test-A (NCT-A), number connection test-B (NCT-B), block design test and digit symbol test. It also recommends the use of psychometric hepatic encephalopathy score (PHES). But, none of test can use in Korea because of the copyright and our own norm. The aim of this study was to make new paper pencil test to evaluate MHE in Korean population.

Methods: New paper pencil test composed of NCT-A, NCT-B, digit span test and symbol digit modality test. The norm of new test was based on 147 healthy individuals between the ages of 20 and 70 years. Another 30 healthy subjects and 33 patients with liver cirrhosis were included as validation cohort. All participants of validation cohort were administered new paper pencil test, critical flicker frequency (CFF) and computer based Stroop test. New paper pencil test was

available at www.hepaticencephalopathy.kr.

Results: The age and education years of the healthy individuals for norm were 46.2 ± 13.1 years and 13.9 ± 3.0 years, with females predominant (55.1%). Each score of NCT-A, NCT-B, digit span test, and symbol digit modality test increased according to age. New paper pencil test for the control group was differed significantly from that of cirrhosis group (1.00 ± 1.68 vs -1.27 ± 3.17, p=0.001) and CFF for the control group was differed significantly from that of cirrhosis group (32.8 ± 3.2 vs 30.9 ± 4.0, p=0.047). But, Stroop test for the control group was not differed significantly from that of cirrhosis group. In an analysis of patients with cirrhosis, new paper pencil test (0.59 ± 1.59 vs -5.00 ± 1.94, p<0.001), CFF (31.8 ± 3.73 Hz vs 28.9 ± 3.94 Hz, p=0.013) and Stroop test (number of commission error, 131.9 ± 5.03 vs 124.1 ± 10.9, p=0.014) distinguished between patients without HEP and with HEP.

Conclusions: The new Korean paper pencil test for the diagnosis of MHE was comparable with previous cognitive function test.

Keywords: Cirrhosis, Diagnosis, Hepatic encephalopathy, Paper pencil test

PS 2-5

Blocking Energy Metabolism by Hexokinase II Inhibitor Overcomes Sorafenib Resistance via Augmenting Endoplasmic Reticulum Stress in Hepatocellular Carcinoma

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Aims: Enhancing sorafenib sensitivity is essential for achieving efficient control of intractable hepatocellular carcinoma (HCC). Considering that sorafenib exerts its effect by endoplasmic reticulum (ER) stress due to hypoxia and energy depletion through anti-angiogenic aspect, hexokinase (HK) II which is an important rate-limiting glycolytic enzyme can be a key player in countervailing the effect of sorafenib. Pyruvate analog 3-bromopyruvate (3-BP), a HK II inhibitor, can promote tumor cell death by augmenting endoplasmic reticulum (ER) stress in human HCC cell lines. We evaluated inhibition of HK II potentiated sorafenib-induced ER stress in HCC cells. We also postulated that simultaneous treatment with sorafenib and 3-BP might synergistically enhance their anti-tumor efficacies against HCCs in vivo models.

Methods: HCC apoptotic cell death was assessed by DAPI staining and apoptotic signaling pathways were explored by immunoblot analysis. Energy depletion was assessed by lactate assay. In vivo ectopic model of HCC was established in BALB-c nu/nu mice intradermally implanted with SNU-761 cells. Moreover, orthotopic model of HCC was established by subcapsular injection of SNU-761 cells via mini-laparotomy in BALB-c nu/nu mice. Sorafenib with/without 3-BP was subsequently administered. The anti-tumor efficacies were evaluated by measuring tumor volumes, bioluminescence imaging, quantifying apoptotic cells, and microvessel densities (MVD). Immunohistochemical (IHC) staining of HK II was performed to explore underlying mechanisms of apoptotic cell death and anti-angiogenesis.

Results: The simultaneous treatment of sorafenib and 3-BP enhanced sorafenib significantly induced apoptosis compared to sorafenib alone. This enhancement was attributed to increased ER stress and JNK activation as compared with sorafenib-treated cells. Lactate assay showed that energy depletion was significantly induced in combination group of sorafenib and 3-BP than sorafenib alone. Moreover, ectopic and orthotopic HCC model of HCC showed that tumor growth was significantly suppressed in mice co-treated with sorafenib and 3-BP, especially bioluminescence signals of sorafenib, 3-BrPA and combination of sorafenib and 3-BrPA groups were reduced to 85.12%, 36.57% and 19.86% of controls, respectively. The percentages of TUNEL-positive cells were significantly increased and MVDs were significantly decreased in those mice. IHC stain revealed that HK II expression in the viable tumor tissue near necrotic region, which was significantly suppressed in mice co-treated with sorafenib and 3-BP.

Conclusions: These results demonstrated that HK II inhibitor enhances sorafenib-induced anti-tumor efficacy via augmenting ER stress in vivo ectopic and orthotopic HCC animal model. Therefore, these combination strategies may efficiently be used in the management of otherwise intractable HCCs.

Keywords: Hepatocellular carcinoma, Sorafenib, Hexokinase II

PS 2-6

TonEBP Promotes Hepatocellular Carcinoma via Promotion of Inflammation

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Aims: Tonicity-responsive enhancer binding protein (TonEBP) is a key transcription cofactor in pro-inflammatory activation of macrophages. TonEBP is involved in inflammatory diseases such as rheumatoid arthritis and atherosclerosis. Since hepatic inflammation is required for the development of hepatocellular carcinoma (HCC), we asked whether TonEBP played a role in HCC.

Methods: We studied liver section and tissue biopsy from patients with HBV-, HCV-, and non-viral-induced HCC, obtained from the University of Ulsan college of Medicine . Levels of protein expression and gene expression was measured by western blot analysis and qRT-PCR. Mice with whole body haplo-deficiency of TonEBP and their wild type littermates (C57BL6 background) were given injection of DEN at 2-week-old age and fed the high fat diet or normal control diet for 30 weeks. Mice of hepatocyte-specific (Albcre +/- or -/- floxed with TonEBP) or myeloid-specific TonEBP deletion(LysM cre +/- or

-/- floxed with TonEBP) and their wild type littermates were injected DEN at 8-week-old age for 48 hrs.

Results: Here we report that TonEBP haplo-insufficiency is resistant not only to diethylnitrosamine (DEN)-induced HCC but also to DEN/high fat diet induced HCC, through attenuation of COX-2 expression and inflammation. In hepatocytes, TonEBP interacts with transcription factor YY1 and histone acetyltransferase p300. This interaction promotes inflammatory stimuli-induced COX-2 expression. Interestingly, hepatic tumor shows higher expression of TonEBP than non-tumor liver in mice and HCC patients. This regulation is associated with miR-223 which expression is down-regulated upon HCC development. In addition, its expression was significantly associated with poor survival of HCC patients after resection.

Conclusions: TonEBP is a novel transcription cofactor in COX-2 regulation through transcription factor YY1. With this mechanism, TonEBP is an independent determinant of HCC and novel target for HCC diagnosis and treatment.

Keywords: TonEBP, Hepatocellular carcinoma, COX-2, HCC recurrence

PS 2-7

EDN1 Expression as a Novel Biomarker for Predicting Sorafenib Responsiveness in Patients with Hepatocellular Carcinoma

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Aims: Predictive biomarkers for sorafenib in hepatocellular carcinoma (HCC) are still not available, despite the modest benefit of sorafenib. We present a novel and sensitive biomarker that can predict the responsiveness to sorafenib.

Methods: A candidate biomarker was found through differential mRNA expression analysis between sorafenib-sensitive and resistant cell lines from The Cancer Cell Line Encyclopedia (CCLE), a public data base. It was tested with in vitro shRNA experiments for its effect to sorafenib-resistance. Consecutive patients with HCC who had undergone sorafenib treatment were included from a prospective cohort and the test set (n=48) and the validation set (n=46) were established. Specimens were archived before sorafenib treatment and a candidate marker was evaluated by the quantitative digital analysis algorithm for immunohistochemistry with regard to their association with response assessment by mRECIST, time to progression (TTP) and overall survival (OS). Further, we performed additional validation study using serum samples before sorafenib treatment obtained from different set of HCC patients (n=40).

Results: Endothelin-1 (EDN1, ET-1) was the only differentially expressed molecule between sorafenib-sensitive and resistant cell lines. Knock-down of EDN1 in HCC cell line increased sorafenib sensitivity. In test set, low EDN1 expression group showed significantly better response to sorafenib (non-progressive disease) compared to high EDN1 expression group (72.7% versus 2.7%, respectively; P<0.001). With the same criteria for the validation set, EDN1 expression maintained predictability for sorafenib responsiveness. Survival analysis showed that high EDN1 expression was an independent prognostic factor for poor OS (hazard ratio [HR], 2.374; 95% confidence interval [CI], 1.051-5.360; P=0.037) and short TTP (HR, 1.907; 95% CI, 1.085-3.350; P=0.025) after sorafenib treatment. We confirmed our results in serum samples of another set.

Conclusions: EDN1 expression can distinguish responders to sorafenib and can be a useful predictive biomarker for sorafenib in HCC.

Keywords: Hepatocellular carcinoma, Sorafenib, Endothelin 1, Biomarker

PS 2-8

Survival Benefit of Liver Resection in BCLC-B Stage Hepatocellular Carcinoma : A Korean Nationwide Multicenter Study with Propensity Score Matching

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Purpose: The recent evidence supporting the survival benefit of liver resection (LR) for Barcelona Clinic Liver Cancer B hepatocellular carcinoma (BCLC-B HCC) is increasing, but remains controversial. Therefore, well designed comparative studies about the results of LR vs. non-surgical treatment for BCLC-B HCC are difficult and still uncommon. The aim of this study was to compare the survival benefit of treatment including LR vs. only non-surgical treatment for BCLC-B HCC between well-matched patient groups.

Methods: We reviewed the database of the Korean Liver Cancer Study Group (KLCSG) selected using random sampling from the nationwide multicenter HCC cohort. The registered patients were diagnosed with HCC between 2003 and 2005 (n=4,520) or between 2008 and 2010 (n=4,966). Among the total 887 patients of BCLC-B HCC (multinodular asymptomatic tumors without an invasive pattern), 83 patients underwent LR as the first or second treatment within 2 years after initial diagnosis (LR group; 9.4%). Control was the group of 599 patients who underwent only non-surgical treatment within 2 years after initial diagnosis (non-LR group; 67.5%). To select well-matched patient groups, propensity score matching was used at 1:1 ratio with covariates at the time of diagnosis including registered timing, gender, age, child class, MELD score, tumor number, tumor size, and under-

lying liver disease. The survival outcomes were compared between the matched groups.

Results: The two groups were well balanced by propensity score matching and 80 patients were matched respectively. In LR group, the patients showed significantly better outcome than in non-LR group. The 1-, 2-, 3-, and 5-year overall survivals were 90.1% vs. 78.7%, 87.6% vs. 47.5%, 75.2% vs. 35.1%, and 54.7% vs. 20.2% in LR vs. non-LR group, each ($p<0.001$). Multivariate Cox proportional hazards regression analysis revealed non-surgical treatments (hazard ratio, 2.974; 95% confidence interval, 1.937 to 4.565, $p<0.001$), low albumin level (≤3.0 g/dl) at the time of diagnosis (hazard ratio, 2.347; 95% confidence interval, 1.014 to 5.433, $p=0.046$), and the largest tumor size greater than 5.5cm (hazard ratio, 1.677; 95% confidence interval, 1.109 to 2.535, $p=0.014$) were significant independent risk factors for overall survival in BCLC-B stage HCC.

Conclusion: In BCLC-B stage HCC, treatment with LR offers a significant overall survival benefit compared with non-surgical treatments.

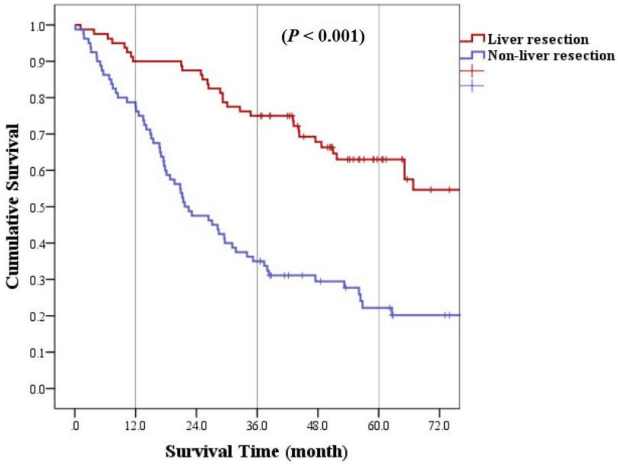

Figure 1. Overall survivals in liver resection vs. non-liver resection groups

Free Paper Presentation

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

1. HBV, Clinical

June 17, 2016 | 13:50-15:30

O - 001

Early Hepatitis B Surface Antigen Seroclearance after Commencement of Antiviral Treatment in Patients with De Novo HBV Reactivation

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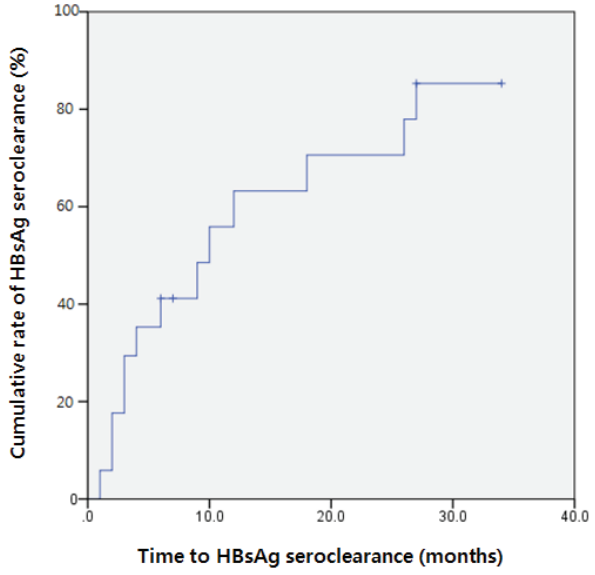
Aims: Hepatitis B virus (HBV) reactivation can occur not only in chronic hepatitis B (CHB) patients, but even in patients with resolved infection, especially in those who had undergone hematopoietic stem cell transplantation (HSCT) or rituximab treatment. We evaluated the virologic-serologic responses after commencement of antiviral treatment in patients with de novo HBV reactivation.

Methods: We reviewed 1,101 consecutive patients treated with rituximab or HSCT who had tested for HBV serum markers at a tertiary center from January 2006 to August 2014. Among them, a total of 341 HBsAg-negative/anti-HBc-positive patients who were followed up with HBV markers were included in the study. Clinical outcomes of the patients with de novo HBV reactivation were then compared with 34 CHB patients who started antiviral therapy during rituximab-based therapy or HSCT for hematological diseases.

Results: Forty-three out of the 341 patients (12.6%) experienced de novo HBV reactivation at median 25.1 months and the cumulative rates were 5%, 13%, and 26% at 1, 2 and 4 years, respectively. The median value of HBV DNA at reactivation was 6.2X106 IU/mL. Twenty-seven patients (62.8%) received antiviral therapy. There was no difference in the complete virologic response rate but significantly higher rate of HBsAg seroclearance was observed in the de novo reactivation group than the CHB group (75% vs. 11.8%, respectively, p<0.001). Early drop in HBsAg titer and higher ALT levels were associated with HBsAg seroclearance. For the de novo reactivation group, the cumulative rates of HBsAg seroclearance were 38% and 60% at 6 and 12 months, respectively, with a median time to HBsAg seroclearance of 6.6 months after antiviral initiation. All of the patients with HBsAg seroclearance except 1 patient without follow-up result also developed anti-HBs antibodies.

Conclusions: De novo HBV reactivation occurs considerably in settings of rituximab-based therapy or HSCT. The early HBsAg seroclearance following antiviral therapy suggests the differential phenotype as well as shorter duration of chronic infection in such patients with de novo HBV reactivation.

Keywords: Hepatitis B virus, Reactivation, Hepatitis B surface antigen, Seroclearance



O - 002

Telbivudine versus Entecavir in Entecavir-Treated Patients with Undetectable Hepatitis B Virus DNA: Randomized Trial

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Aims: Recent study suggested that telbivudine (LdT) may have similar efficacy in reducing Hepatitis B surface antigen (HBsAg) titer compared with pegylated interferon. We aimed to investigate whether telbivudine could further decrease HBsAg titer in the patients who maintained undetectable serum hepatitis B virus (HBV) DNA after initial entecavir (entecavir) treatment.

Methods: In this open-label, single-center study, patients were randomly assigned 1:1 to switch to telbivudine (n=47) or continue with entecavir (n=50). HBV DNA, HBsAg titer, and liver biochemistry were performed at weeks 0, 12, 24, and 48. Mutational analysis was checked at the time of HBV DNA relapse.

Results: Median baseline HBsAg levels were comparable between LdT and entecavir groups (3.43 vs. 3.40 log10IU/mL, P=0.427). At 48 weeks of follow-up, median HBsAg titer was not significantly different between LdT and entecavir arm (3.37 vs. 3.39 log10 IU/mL, P=0.653). The decline in mean HBsAg over 48 weeks was also similar (-0.03 ± 0.14 vs. -0.05 ± 0.11 log10IU/mL, P=0.568). Viral breakthrough (VBT), mostly along with genotypic resistance, was significantly more frequent in LdT group compared with those with entecavir (19.1% vs. 0%, P=0.001 for VBT, and 14.9% vs. 0%, P=0.005 for emergence of antiviral resistance). One patient developed myopathy on LdT treatment and recovered after discontinuation of drug.

Conclusions: Sequential therapy using entecavir followed by LdT did not show additional benefit on reducing HBsAg titer compared with

entecavir continuation. Switching to LdT was associated with higher rate of VBT and resistance development during 48 weeks.
Keywords: Hepatitis B, Hepatitis B surface antigen, Telbivudine, Entecavir

O - 003

Long-term Nucleotide Analogue Treatment Has Increase of Renal Toxicities Compared to Entecavir Treatment in Patients with Chronic Hepatitis B

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Background/Aims: Nucleotide analogues (adefovir and tenofovir) have concerns of renal toxicities. Chronic hepatitis B patients treated with adefovir (ADV) based regimens are changing to tenofovir (TDF) based treatments in Korea due to national imbursement policies. The aim of this study is to reveal longterm renal effects of ADV experienced TDF treated patients compared to entecavir (ETV) treated patients.
Methods: In this retrospective single center study, we selected 87 patients who were treated with ADV and subsequent TDF from June 2008 to Dec 2013. And they were matched by treatment duration of ADV plus TDF (ADV+TDF group) with ETV treated patients, and treatment duration of tenofovir only (TDF group) with ETV treated patients. We analyzed creatinine increase over 0.5 mg/dL, GFR decrease under 25%, phosphorus decrease under 2.0 mg/dL, and dose reduction of antiviral agents.
Results: Median follow-up period were 60.0 months for ADV+TDF group and 24.0 months for TDF group, respectively. There were no difference in creatinine increase (5.7% and 2.3%, P=0.25), but more GFR decrease (31.0% and 14.9%, P=0.02) events occurred during follow-up in ADV+TDF group compared to ETV group, respectively. Dose reduction of antiviral treatments was higher in ADV+TDF group compared to ETV group, but not significantly different (6.9% and 2.3%, P=0.27), respectively. There were no difference in creatinine increase (1.1 and 3.4%, P=0.30), and GFR decrease (10.3 and 12.6, P=0.59), but more hypophosphatemia (12.6% and 1.2%, P<0.01) events occurred during follow-up in TDF group compared to ETV group, respectively.
Conclusions: Nucleotide analogues showed significant decrease in GFR compared to ETV, and TDF showed significant hypophosphatemia development compared to ETV. Although there was no significant decrease in GFR at TDF treatment duration, clinicians should be aware of renal toxicity development, and further long term study needs to be performed in this population.
Keywords: Nucleotide analogue, Renal toxicity, Tenofovir, Entecavir

O - 004

Combined Use of AST to Platelet Ratio Index and Fibrosis-4 Score Can Risk Stratify Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients with Low Level Viremia

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Aims: The prognosis of chronic hepatitis B virus (HBV) infected patients showing low level viremia (HBV DNA < 2,000 IU/mL) are generally excellent, yet, those with cirrhosis are still at risk for developing hepatocellular carcinoma (HCC). Liver biopsy is the gold standard to differentiate cirrhosis in this population, yet, due to its invasiveness, many had to rely on noninvasive liver fibrosis predictors. We tested whether simple noninvasive liver fibrosis predictors, the AST to platelet ratio index (APRI) and the Fibrosis-4 (FIB-4), can effectively risk-stratify HCC risk in patients with low level viremia.
Methods: A retrospective cohort of 1,380 CHB patients with low level viremia (HBV DNA < 2,000 IU/mL) was assessed for the development of HCC. Cirrhosis was defined clinically by cirrhotic configuration, varix, thrombocytopenia with splenomegaly. Based on APRI and FIB-4 score, patients were divided into two groups based on known cutoff (0.5 for APRI and 1.45 for FIB-4), which has shown high negative predictive value for advanced fibrosis.
Results: During a median 5.7 years (range: 1.0-9.2 years) of follow-up, HCC developed in 65 patients. The HCC incidence rate was higher for cirrhotic patients (40/237 patients, 16.7% at 5-years), but was not null for non-cirrhotic patients (25/1,143 patients, 1.9% at 5-years, p < 0.001). The AUROCs for the HCC development at 3/5 years was 0.78/0.73, 0.79/0.78, and 0.79/0.76 for cirrhosis, APRI and FIB-4, among overall cohort, respectively, and was 0.73/0.83 and 0.83/0.89 for APRI and FIB-4, among non-cirrhotic patients. When stratified by APRI and FIB-4, the 5-year cumulative HCC incidence rate was 13.7%, 2.8% and 1.4% for both high, any high, and both low APRI and FIB-4, among overall cohort (p < 0.001), and was 11.5%, 2.4% and 0.2% for both high, any high, and both low APRI and FIB-4, among non-cirrhotic patients (p < 0.001), respectively.
Conclusions: The combined use of APRI and FIB-4 can effectively risk stratify individuals risk for HCC, and can be useful in clinical practice for the HCC prediction among patients with low level viremia, including those without clinical evidence of cirrhosis.
Keywords: Hepatocellular carcinoma, Low level viremia, AST to platelet ratio index, Fibrosis-4 score

O - 005

Comparison of Clinical Outcomes of Antiviral Treatment in Compensated Liver Cirrhosis : Entecavir vs. Tenofovir

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Aims: Long-term suppression of hepatitis B virus (HBV) DNA by antiviral agents is thought to reduce HCC development and improve hepatic fibrosis in chronic hepatitis B. Entecavir (ETV) and tenofovir (TDF) are first-line nucleos(t)ide analogs (NA) for chronic hepatitis B (CHB)

due to their high potency and low genetic barrier to resistance. However, it is not known whether there is any difference in reducing the risk of HCC between the two NAs. The goal of this retrospective cohort study was to compare the incidence of HCC and assess whether hepatic fibrosis was improved in HBV related-compensated liver cirrhosis (LC) on these NAs.

Methods: We retrospectively analyzed 213 NAs naïve HBV-related compensated LC patients who visited our hospital between 2007 and 2013 and started entecavir or tenofovir. The primary objective of the study is to compare the incidence of HCC in 118 ETV-treated and 95 TDF-treated patients. The secondary outcome is to observe changes of non-invasive fibrosis indexes (aminotransferase-to-platelet ratio index [APRI] and FIB-4) through long-term antiviral therapy.

Results: The mean duration of antiviral therapy was 3.4 years (ETV 4.3 years and TDF 2.4 years). The cumulative probabilities of achieving virologic response at week 96 were 93.2% and 95.8% in ETV group and TDF group, respectively (p=0.042). After a median 1.3 years of treatment, 14 cases of HCC were diagnosed: 7 in the ETV group and 7 in the TDF group (5.9% vs. 7.4%, p=0.674). In both treatment group, there were significant differences in the reduction of APRI and FIB-4 scores through long-term antiviral therapy.

Conclusions: There is no difference in the HCC incidence between HBV related-compensated LC patients on ETV and TDF. Long-term antiviral therapy shows improvements in APRI and FIB-4 score.

Keywords: Compensated liver cirrhosis, Hepatocellular carcinoma, Entecavir, Tenofovir

O - 006

Long-term Clinical Outcome of Tenofovir-based Therapy versus Lamivudine Plus Adefovir Combination Therapy in Patients with Lamivudine-resistant Chronic Hepatitis B: Propensity Score Analysis

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Aims: Currently, for patients with lamivudine (LAM)-resistant CHB infection, switching to or adding on tenofovir (TDF) are considered as therapeutic options. Little data are available on the comparison of long-term efficacy of TDF-based rescue therapy and LAM/adefovir (ADV) combination therapy in patients with LAM-resistant chronic hepatitis B infection.

Methods: One hundred ninety-seven patients received LAM plus ADV, and 53 patients received TDF-based rescue therapy. Patients who received TDF-based rescue therapy were treated with TDF alone (n = 30) or TDF/LAM combination (n = 23). A matched study population was constructed to compare the antiviral efficacy of TDF-based rescue therapy and LAM/ADV combination therapy by a propensity score analysis.

Results: Eighty-eight patients from the LAM/ADV therapy group and 44 patients from the TDF based rescue therapy group were selected after matching propensity score with 2:1 ratio. Virologic response (VR) was observed in 97.7% (43/44) of patients in the TDF group and in 79.5% (70/88) of the patients in the LAM/ADV group. The rate of VR in the TDF group was higher than that of the LAM/ADV group (P = 0.004). To determine the impact of baseline viral load on the response to treatment, a post hoc exploratory analysis was performed. Among the patients with baseline HBV DNA level > 104 IU/mL, a higher proportion of patients in the TDF group than in the LAM/ADV group achieved VR (95.5 vs. 65.9%, P < 0.001). In contrast, among patients with baseline HBV DNA level < 104 IU/mL, VR rates were not different between the LAM/ADV and TDF groups (73.0 vs. 99.5% at month 12, and 93.2 vs. 100% at month 24; log rank P = 0.885). No major clinical side effects were reported during the treatment with either TDF or LAM/ADV groups.

Conclusions: long-term efficacy of TDF-based rescue therapy would be more superior to the LAM/ADV combination therapy, in the management of LAM- resistant patients. However, in the patients with baseline HBV DNA level <104 IU/mL, LAM/ADV combination therapy was as effective as TDF-based rescue therapy in maintaining the viral suppression.

Keywords: Tenofovir, Lamivudine plus adefovir, Lamivudine resistance, Chronic hepatitis B

O - 007

Hepatitis B Surface Antigen Titer Is a Good Indicator of Durable Viral Response after Off-treatment of Entecavir for Chronic Hepatitis B

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Aims: Definite guideline for stopping antiviral therapy for chronic hepatitis B (CHB) is not clarified yet. Previous studies suggested that HBsAg titer is correlated with covalently closed circular DNA. Therefore, HBsAg titer might be a good indicator for off-treatment. This study was performed to determine the relationship between HBsAg titer and CHB relapse after off-treatment of entecavir (ETV).

Methods: Patients in whom ETV was discontinued after serum HBV with or without HBeAg clearance for more than 12 months and who measured HBsAg titer at off-treatment were enrolled. HBV DNA reactivation was defined as increase of serum HBV DNA level >2000 IU/mL, while CHB relapse was defined as HBV DNA reactivation and increase of serum ALT level >2XULN.

Results: Forty-four patients were enrolled. Age was 44.6±11.4 years and 28 patients (63.6%) were men. Baseline HBeAg was positive 25 patients (56.8%) and serum HBV DNA level was 6.8±1.3 log10 IU/mL. ETV was discontinued after 34.7±19.0 months of treatment. In HBeAg-positive CHB patients, ETV was discontinued after 37.0±20.2 months of treatment, which was 31.0±19.5 and 23.4±16.1 months after serum HBV DNA and HBeAg clearance, respectively. In HBeAg-negative CHB patients, ETV was discontinued

after 31.6±17.4 months of treatment, which was 27.1±17.7 months after serum HBV DNA clearance. HBsAg titer at off-treatment was 3.0±1.0 log10 IU/mL, which was <2, 2~3, and >3 log10 IU/mL in 5 (11.4%), 11 (25.0%), and 28 (63.6%) patients, respectively. After off-treatment, HBV DNA reactivated in 38.7% and 66.2% and CHB was relapsed in 4.7% and 42.3% at 6 and 12 months after off-treatment, respectively. HBsAg titer at off-treatment was significantly associated with HBV DNA reappearance (P=0.010) and CHB relapse (P=0.010).

Conclusions: HBsAg titer at off-treatment is closely related with HBV reactivation and CHB relapse. HBsAg titer is considered as an excellent indicator of durable viral response after off-treatment.

Keywords: Hepatitis B virus, Hepatitis B surface antigen, Relapse, Off-treatment

O - 008

Change in Alpha-fetoprotein Levels in Chronic Hepatitis B Patients on Tenofovir Therapy

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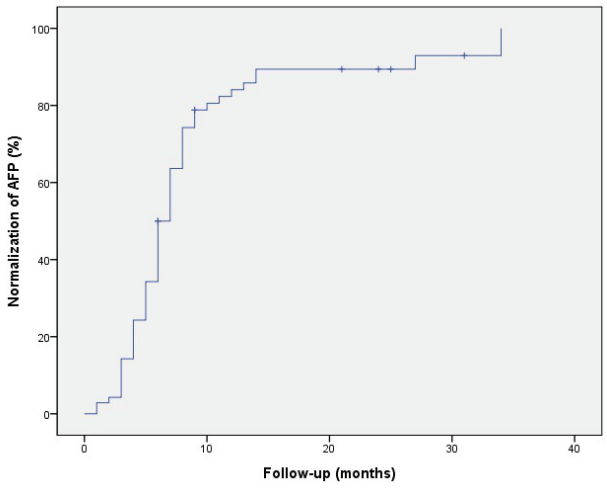
Aims: Alpha-fetoprotein (AFP) has been widely used as a biomarker for hepatocellular carcinoma (HCC). However, AFP levels may elevate in chronic hepatitis B (CHB) patients who are candidates for oral nucleos(t)ide analogue (NA) therapy. The response of AFP levels to tenofovir therapy is largely unknown. The aim of this study was to investigate factors related with AFP elevation and effects of tenofovir on AFP changes in CHB patients.

Methods: The serial changes in AFP levels were analyzed in a retrospective cohort of 262 naïve CHB patients who received over six-months of treatment with tenofovir.

Results: Among the 262 patients, 71 showed high pre-treatment AFP values (> 10 ng/dl), with mean and SD being 145.7 and 302.6 ng/dl, respectively. When baseline parameters were statistically evaluated in relation to the AFP value, albumin were significantly lower ($p < 0.001$) and prothrombin time, bilirubin and aspartate aminotransferase (AST) levels were significantly higher in the high AFP group ($p = 0.002$, 0.001 and 0.008, respectively). Post-treatment AFP was significantly reduced in both the high AFP (mean, 4.1 to 2.9 ng/dl [$p < 0.001$]) and low AFP group (mean, 147.6 to 7.0 ng/dl [$p < 0.001$]). Kaplan-Meier analysis showed that normalization of AFP occurred in 62 patients (88.6%) during follow-up, with a mean normalized time of 9.1 months. There were 7 patients of newly diagnosed HCC during follow-up. Post-treatment AFP was significantly reduced (mean, 53.7 to 7.0 ng/dl [$p < 0.043$]).



Conclusions: In candidates for NA therapy, elevated AFP levels are associated with more advanced stage of CHB. Tenofovir has shown efficacy in reducing AFP levels, even in newly diagnosed HCC patients.

Keywords: Alpha-fetoprotein, Chronic hepatitis B, Tenofovir, Hepatocellular carcinoma

O - 009

Prevention of Vertical Transmission with Antiviral Agent during Late Pregnancy in Highly Viremic Mothers Infected with Hepatitis B Virus

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Aims: In spite of the immunoprophylaxis against hepatitis B virus (HBV), mother-to-child transmission (MTCT) of HBV occurs nearly 20% of infants born to highly viremic hepatitis B mothers. But, there are limited data on the outcome in pregnant women after antiviral use during late pregnancy to reduce MTCT. This study was performed to evaluate the efficacy of antiviral agents on preventing MTCT of HBV in Korea.

Methods: We retrospectively reviewed medical records of hepatitis B infected pregnant women treated with antiviral agents in late pregnancy to prevent MTCT in six tertiary hospitals between 2011 and 2015. 39 pregnant women who had received antiviral therapy of telbivudine or tenofovir which belongs to pregnancy category B during late pregnancy (24-32week) were enrolled. 41 babies were checked hepatitis B surface antibody (HBsAb) positivity after 7 months of delivery.

Results: Median age at delivery was 32 (range, 22-40) years, mean HBV DNA before antiviral therapy was 8.4 (range, 6.6-9.4) log10 copies/mL. Eight women had previous exposure to antiviral therapy. Ten women were treated with tenofovir and twenty nine women with telbivudine. Median duration of antiviral therapy before delivery was 58 (range, 23-100) days, mean HBV DNA at birth after using antiviral agent during late pregnancy was 4.8 (range, 2.5-6.4) log10 copies/mL. Both tenofovir and telbivudine treatments in pregnant

Table 1. Baseline characteristics and clinical outcomes.

	all patients (n = 39)	TDF (n = 10)	LdT (n = 29)
Demographics			
Age at delivery, years	32 (22-40)	31.5 (29-35)	32 (22-40)
prior pregnancy, n (%)	11 (28.2%)	3 (30%)	8 (27.5%)
Previous exposure to antiviral Tx, n (%)	8 (20.5%)	2 (20%)	6 (20.6%)
Baseline characteristics			
HBV DNA at initiation, log copies/mL	8.4 (6.6-9.4)	8.3 (6.6-9.4)	8.4 (7.0-9.3)
HBe Ag positivity, n (%)	35 (89.7%)	8 (80%)	27 (93.1%)
Baseline ALT (U/L)	21 (10-645)	22 (13-371)	19 (10-645)
Clinical outcomes			
HBV DNA at delivery, log copies/mL	4.8 (2.5-6.4)	4.7 (2.6-6.4)	4.9 (2.5-6.3)
Treatment duration, days	58 (23-100)	59 (37-83)	57 (23-100)
Vertical transmission, n (%)	2 (4.8%)	2 (20%)	0 (0%)

women were associated with significant serum HBV DNA reduction ($P<0.05$). Among 41 babies (two cases of twin), hepatitis B surface antibody (HBsAb) was not detected in two infants, confirmed to be infected with HBV in tenofovir treatment group only.

Conclusions: Administrating antiviral agents during late pregnancy in chronic hepatitis B pregnant women with high viremia could reduce perinatal HBV transmission successfully, and also helped giving rise to HBsAb in almost infants. Additional studies are needed to investigate the two case of MTCT despite effective maternal viral load reduction.

Keywords: Vertical transmission, HBV, Pregnancy, Antiviral agent

O-010

Tiny Echogenic Nodule (TEN) Detected in High-frequency Spatial Compound Ultrasonography Is a New Specific Image Marker for Chronic Hepatitis B Virus Infection

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Aims: Chronic hepatitis B virus (HBV) infection is the most important cause of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in endemic areas throughout the world. Liver ultrasonography (US) is usually performed with 3-4 MHz frequency probe to evaluate fibrosis stage and to screen early HCC for HBV carriers. Its maximum resolution to detect solid nodule in liver is approximately 5mm in diameter. Because of its weak penetrating power, high frequency 5-12 MHz probe is limited to deciding the surface irregularity of liver. However, we have noticed with the 9 MHz B-mode US (HF-9) that various sizes of tiny echogenic nodule (TEN) are frequently seen in liver among patients having chronic liver disease (CLD). We analyzed the significance of TEN being observed in the HF-9 image.

Methods: HF-9 was performed in two or three intercostal views with GE LogiQ-E9. TEN was arbitrarily defined as an echogenic nodule less than 5mm seen in the HF-9. Liver stiffness was measured in every case with real-time shear wave elastography (SWE), together with the conventional 3 MHz US. Fatty liver grading was also performed. Liver biopsy was available in some cases with TEN.

Results: A total of 817 CLD subjects (533 men and 284 women; age, 53.8±11.8 old years) were analyzed. Etiology consisted of HBV (n=533), hepatitis C virus (HCV, n=30), alcoholic liver disease (ALD, n=77), non-alcoholic fatty liver (NAFL, n=102) and others (n=75). The conventional US diagnosis consisted of 288 normal, 198 borderline, 163 fibrotic and 168 cirrhotic livers. TENs were observed in 134 cases (16.4%), but the majority of them (91.8%, n=128) were HBV carriers. In terms of etiology, TEN was seen in 23.1% of HBV, 6.7% of HCV, 4.5% of ALD, 0% of NAFL and 2.2% of others, respectively. In the ANOVA and multiple regression analysis of HBV carriers without ALD or moderate-to-severe degree of NAFL (n=463), male and the US evidence of CLD appeared to be significant as predictive factors for the TEN. Especially, the HF-9 image finding of CLD such as the number and irregular arrangement and thickening of tiny-to-small echogenic band was more closely associated with TEN than the degree of stiffness determined by elastography. The TEN itself was too small to be exactly characterized in the biopsy specimen, although surrounding liver tissue shows various degrees of necro-inflammation, fatty change and sometimes dysplastic cells.

Conclusions: Our results suggest that TEN is a new and specific image marker for HBV carriers. Furthermore, TENs tend to be significantly associated with the fibrotic background, so that high-frequency spatial compound US should be a part of liver sonography analysis for CLD. Further study is necessary to determine the pathologic characteristics of TEN and its prognostic implication for the long-term outcome of HBV carriers.

Keywords: Ultrasonography, Chronic Hepatitis B, Liver Fibrosis, Hepatocellular carcinoma

2. HCV, Clinical

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O-011

Establishment of Full Genomic Length Resistance-Associated Variant Genotype 2 Hepatitis C Viruses and Applications for Future Therapeutic Strategies

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Aims: Several directly acting antiviral agents (DAA) were currently approved for the treatment of chronic hepatitis C (CHC). Although DAA therapies are associated with better tolerability and improved response rates, occurrence of drug resistance has been the drawback. The aim of the present study is to develop full-length resistance associated variants (RAV) HCV culture systems to evaluate the efficacy and the cross resistance of current antiviral drugs for future therapeutic strategies.

Methods: Resistance associated substitutions on NS3 (A156T, D168V), NS5A (L31V, Y93H, L31V+Y93H), and NS5B (S282T) domains were generated by site directed mutagenesis and cloned into genotype 2a J6/JFH1 HCV plasmid with or without luciferase gene. After In

vitro RNA transcription, RNAs of RAV were transfected into Huh 7.5.1 cells. HCVcc in the supernatants were collected and used for the reinfection and treatment experiment to confirm drug susceptibility. We performed HCV core staining and Renilla luciferase assays to assess treatment response to multiple DAAs and other antiviral drugs with different mechanism of action after transfection or infection of RAVs.

Results: DAAs in the same classes shared cross resistance to corresponding RAVs: boceprevir, telaprevir, simeprevir, and asunaprevir to NS3 RAVs; daclatasvir and ledipasvir to NS5A RAVs; sofosbuvir to NS5B RAV. However, DAAs of the other classes effectively suppressed RAVs as well as wild type. All the RAVs were sensitive to drugs with different action of mechanism including interferon alfa, ribavirin, cyclosporine (cyclophilin inhibitor) or chlorcyclizine (entry inhibitors).

Conclusions: We developed full-length RAV HCV culture systems based on genotype 2a strain. This system will be useful to assess antiviral response of drugs with different action of mechanisms. Combination of different classes of DAA or new drugs with different action mechanisms (e.g. cyclophilin inhibitor or entry inhibitors) should be a future therapeutic strategy for overcoming drug resistance in the treatment of CHC.

O-012

Asian Patients with Genotype 1 HCV Achieve 99% SVR with 12 Weeks of Ledipasvir/Sofosbuvir: Integrated Analysis of Phase 3 Studies

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Background: Similar to the United States and Europe, the majority of patients with chronic HCV infection in Japan, Korea, and Taiwan are infected with HCV genotype (GT) 1. However, important differences in viral and host characteristics exist between the infected populations in these regions, including age, BMI, IL28B genotype and HCV GT1 subtype. The aim of this integrated analysis is to evaluate the efficacy and safety of ledipasvir/sofosbuvir (LDV/SOF) in a large cohort of Asian patients with chronic GT1 HCV infection.

Methods: This analysis combines data from subjects enrolled in two Phase 3 trials: GS-US-337-0113 (Japan) and GS-US-337-0131 (Korea and Taiwan) evaluating 12 weeks of LDV/SOF (90mg/400mg) in treatment-naïve and treatment-experienced adults with chronic GT1 HCV infection. The primary efficacy endpoint was SVR12.

Results: Overall, 349 subjects were enrolled in Korea, Taiwan, and Japan, 67 (19%) had cirrhosis. The majority were female (58%), treatment-experienced (51%), GT1b infected (94%), and IL28B CC (62%). The mean age (range) was 57 (18-80) years old, BMI 24 (17-38) kg/m2, and HCV RNA was 6.6 (3.7-7.6) log10 IU/mL. HCV NS5A RAVs were detected in 23% (80/343) of subjects at baseline. The overall SVR12 rate was 99% (346/349); 2 subjects relapsed and 1 subject prematurely discontinued treatment. All treatment-experienced subjects with cirrhosis (45/45) achieved SVR12. NS5A RAVs were detected at the time of relapse but no NS5B RAVs were detected. Serious AE and treatment discontinuations were rare (<2%). Adverse events were generally mild in severity. No significant laboratory abnormalities were observed.

Conclusions: A single tablet regimen of LDV/SOF administered once daily for 12 weeks is highly effective and well tolerated in Asian patients with chronic GT1 HCV infection, including those with compensated cirrhosis. Prior HCV treatment experience and the presence of cirrhosis did not impact treatment response.

Keywords: Ledipasvir, Sofosbuvir, Asian, Genotype 1

O-013

Asian Patients with Genotype 2 HCV Achieve 98% SVR with Sofosbuvir and Ribavirin: Integrated Analysis of Phase 3 Studies

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Background: Chronic hepatitis C (CHC) infection presents a significant burden on public health in Asia. Among patients with CHC, 20-30% in Japan and 50% in Korea and Taiwan are infected with hepatitis C virus (HCV) genotype (GT) 2. Sofosbuvir (SOF) in combination with ribavirin (RBV) is the first all-oral regimen for treatment of HCV GT2 infection. The aim of this integrated analysis is to characterize the efficacy and safety of SOF+RBV in a large cohort of Asian patients with HCV GT2 infection from two Phase 3 trials, GS-US-334-0118 (Japan) and GS- US-334-0115 (Korea and Taiwan).
Methods: In both studies, adults with chronic GT2 HCV infection received SOF (400mg) combined with RBV for 12 weeks. The primary efficacy endpoint was Sustained Virologic Response measured 12 weeks after the last dose of study drug (SVR12).
Results: Overall, 369 patients were enrolled (n=129 Korea, n=87 Taiwan, and n=153 Japan), of which 64% (238/369) were treatment naïve and 36% (131/369) were treatment experienced. Mean age (range) was 55 (22-82) years, 44% male (164/369), 82.1% (303/369) IL28B-CC, and 12% (43/369) had cirrhosis. The overall SVR12 rate was 98% (360/369). Similar high rates of SVR12 were seen in treatment-experienced (98%, 128/131), patients ≥65 years old (96%, 73/76), and those with cirrhosis (98%, 42/43). Nine patients did not achieve SVR12 (1 partial responder, 6 relapsers, 2 lost to follow up). Adverse events were generally mild to moderate. Laboratory abnormalities were infrequent and consistent with the safety profile of RBV. No AEs led to treatment discontinuation.
Conclusions: Asian patients with chronic GT2 HCV infection achieved high rates of SVR12 with 12 weeks of SOF+RBV. The regimen was safe and well-tolerated with no treatment discontinuations due to AE. The data suggest that SOF+RBV may offer an improved, IFN-free treatment for Asian patients with chronic GT2 HCV infection.
Keywords: Sofosbuvir, Phase 3, Asian, Genotype 2

O - 014

Integrated Safety and Tolerability of Daclatasvir plus Asunaprevir in Patients with Chronic HCV Genotype 1b Infection

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Aims: The combination of daclatasvir (DCV) plus asunaprevir (ASV) has demonstrated high sustained virologic response (SVR) rates and is generally well tolerated in clinical studies. This integrated analysis evaluated the safety profile of DCV (60mg once daily) and ASV (100mg softgel capsule or 200mg tablets twice daily in genotype 1b (GT1b) infected patients enrolled in four phase 3 and two phase 2 clinical studies conducted globally, including Asia.
Methods: Integrated safety data from 1218 treatment-naive or treatment-experienced patients were analyzed for adverse events (AEs), serious AEs, discontinuations due to AEs and grade 3/4 AEs and laboratory abnormalities reported on-treatment.
Results: Patients were 58% female, median age was 58 years and 23% had compensated cirrhosis. DCV+ASV was associated with infrequent serious AEs and discontinuations due to AEs (Table). Twelve patients reported treatment-related serious AEs. The most common AEs (any grade) were diarrhea, nausea, fatigue, and headache. One patient died due to coronary heart disease (not treatment-related). The most common grade 3/4 laboratory abnormalities were aminotransferase elevations (more frequent among Japanese patients); however, all grade 3/4 laboratory abnormality occurred in <5% of patients overall. Grade 3/4 total bilirubin elevations were reported in <1% of patients. The DCV+ASV safety profile was similar in patients with or without cirrhosis.
Conclusions: DCV+ASV was generally well tolerated across global non-Asian patient populations and in Asian patients from Japan, mainland China, Korea, and Taiwan.
Keywords: Chronic HCV, Genotype 1b, Safety, Tolerability, Daclatasvir, Asunaprevir

Patients, n (%)	Global[a]			Japan[b]				Asia[c]	Total[d,e]
	028 N=645	011 N=18	Total N=663	031 N=141	017 N=33	026 N=222	Total N=396	036 N=159	N=1218
Death	0	0	0	0	0	0	0	1 (<1)	1(<0.1)
Serious AEs[f]	39 (6)	1 (6)	40 (6)	6 (4)	3 (9)	13 (6)	22 (6)	5 (3)	67 (6)
AEs leading to discontinuation	10 (2)	0	10 (2)	7 (5)	2 (9)	11 (5)	20 (5)	2 (1)	32 (3)
Grade 3/4 AEs	50 (8)	1 (6)	51 (8)	21 (15)	6 (21)	37 (17)	64 (16)	20(13)	135(11)
Emergent grade 3/4 laboratory abnormalities									
Hemoglobin <9 g/dL	1 (<1)	0	1(<1)	0	0	7 (3)	7 (2)	1 (<1)	9 (1)
Platelets <50 x 10^9 cells/L	11 (2)	0	11 (2)	0	0	4 (2)	4 (1)	16 (10)	31 (3)
Neutrophils <0.75 x 10^9 cells/L	9 (1)	0	9 (1)	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)	12 (1)
ALT >5 xULN	15 (2)	1 (6)	16 (2)	16 (11)	4 (9)	16 (7)	36 (9)	2 (1)	54 (4)
AST >5 xULN	12 (2)	1(6)	13 (2)	7 (5)	3(7)	12 (5)	22 (6)	3 (2)	38 (3)
Total bilirubin >2.5 xULN	3 (0.5)	0	3 (<1)	0	0	2 (1)	2(<1)	1 (<1)	6 (<1)

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Includes studies: AI447028 (includes non-Asian, N=492; Asian, N=153), AI447011 (includes non-Asian, N=16, Asian, N=2)
[b] Includes studies: AI447031, AI447017, AI447026 (all patients were Japanese)
[c] Includes studies: AI447036 (includes mainland China, N=127; Korea, N=17; Taiwan, N=15.)
[d] AEs reported during rescue therapy (DCV plus ASV and pegIFN plus ribavirin) were not included in this analysis.
[e] Only includes patient on the recommended DCV plus ASV dose (DCV 60 mg QD and the ASV 200 mg BID tablets or 100 mg BID softgel capsules)
[f] Treatment-related serious AEs in 12 patients included pyrexia (n=5), hypochondriasis (n=1), aminotransferase elevation (n=5), bilirubin elevation (n=1) , C-reactive protein increase (n=1), myasthenia gravis (n=1), atrial fibrillation (n=1) and hepatic enzyme increase (n=1); some patients experienced >1 serious AE.

O - 015

Hepatitis C Virus Genotype 3 Is Associated with the Development of Hepatocellular Carcinoma and Mortality in Patients with Cirrhosis

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Aims: Hepatic C virus (HCV) genotype 3 infection is the most difficult form of HCV to treat, with a more rapid progression to fibrosis and cirrhosis compared with other genotypes. The aims of this retrospective observational study were to elucidate the impact of genotype 3 infection on hepatocellular carcinoma (HCC) development and overall mortality in patients with HCV-related cirrhosis, compared to HCV genotype 1 and 2 in the Gyeongnam Province, located on the southeast coast of Korea.

Methods: A total 153 patients with HCV-related cirrhosis were included between January 2005 and December 2014. Among these, 74 had genotype 1, 55 genotype 2, and 24 patients had genotype 3 infection.

Results: The prevalence of genotype 3 in HCV-related cirrhosis was 16%. Individuals at risk for genotype 3 infection were young, male gender, and people who inject drugs. During median a median follow-up 40.1 months, 38 patients developed HCC, and 23 patients died. The incidence of HCC development and overall mortality was significant higher in patients with genotype 3 compared to patients with genotype 1 and 2 in the log rank test. Despite being younger, HCV genotype 3 was a independent risk factor for HCC development (adjusted hazard ratio [HR] = 2.55) and overall mortality (adjusted HR = 3.69) on multivariate anlalysis. After exclusion of patients with achieved sustained virologic response, the incidence of HCC development and overall mortality was significant higher in patients with genotype 3 compared to patients with no genotype 3.

Conclusions: HCV genotype 3 infection is associated with an increased risk of HCC and overall mortality in patients with cirrhosis after adjusting with confounding factors.

Keywords: Hepatitis C virus, Genotype 3, Hepatocelular carcinoma, Mortality

O-016

Long-term Recipient and Graft Survival after Kidney Transplantation in Recipients with Hepatitis C Virus Infection

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Aims: The prevalence of hepatitis C virus (HCV) infection among kidney transplant (KTx) recipients is higher than that in the general population. With the advent of highly effective antiviral regimens against HCV, the optimal management strategies for KTx recipients continue to evolve. We examine the impact of HCV infection on long-term patient and graft survival after KTx.

Methods: The UNOS OPTN database was queried for all adult KTx recipients in USA between January, 2004 and December 2006. A propensity score (PS) was created, which was used to select a matching HCV-negative control for each HCV-positive recipient. The survival analysis was conducted to evaluate recipient and death-censored graft survival.

Results: Out of 35,557 adult primary KTx recipients during the study period, 1,470 (4.4%) were positive for anti-HCV at KTx. Overall, when compared to HCV- recipients, HCV+ patients were more likely to be older, male, and American African and more likely to have HLA mismatch, longer length of time on dialysis. PS matching selected 1,374 HCV+ and - pairs. The Kaplan-Meier estimates for recipient survival at 1, 5, 10 year was 94.7%, 79.5%, and 58.2% for HCV+ patients and 95.8%, 84.4%, and 66.3% in HCV- patients, respectively ($p<0.01$). Death-censored graft survival at 1, 5, 10 years was 94.4%, 76.8%, and 57.0% in HCV+ patients and 94.0%, 81.1%, and 66.4% in HCV- recipients, respectively ($p=0.15$). The risk of death due to infection was significantly higher in HCV+ than in HCV- recipients (hazard ratio [HR]=1.64, 95% confidence interval [CI], 1.12-2.36). The incidence of death due to liver failure 0.23% per year among HCV+ recipients, whereas there was no death from liver failure among HCV- recipients. The risk of graft failure due to recurrent disease was higher in HCV+ than in HCV- recipients (HR=2.00; 95% CI, 1.06-3.78). Multivariable Cox regression showed that HCV+ is associated with a higher risk of death (HR=1.50, 95% CI=1.28-1.75) and death-censored graft failure (HR=1.26, 95% CI=1.08-1.47).

Conclusions: HCV infection was associated with decreased long term recipient and graft survival. This analysis suggests that successful antiviral treatment before or after KTx in chronic kidney disease with HCV infection may impact the improved recipient and graft survival.

Keywords: Hepatitis C, Kidney transplantation, Survival

O-017

Prevalence of Hepatitis C Virus Variants Resistant to NS5A Inhibitor in the Korean Population

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Aims: Hepatitis C virus (HCV) is the second most prevalent cause of chronic hepatitis and related morbidity in Korea. A novel combination therapy of daclatasvir (NS5A replication complex inhibitor) and asunaprevir (NS3 protease inhibitor) has shown promising results for genotype 1b chronic hepatitis C. But the response rates have been

Table 1. Prevalence of amino acids substitutions for the resistance to NS5A inhibitor.

	L31	Y93	HCV RAV
Positive (%)	13 (2.9)	39 (8.7)	51 (11.4)
Negative (%)	427 (92.4)	388 (86.6)	376 (83.9)

Table 2. Baseline characteristic of the patients infected with HCV according to the existence of drug-resistant variants.

	HCV RAV		P value
	Positive (%)	*Negative (%)*	
Sex			
male	28 (12.9)	189 (87.1)	0.534
female	23 (11.0)	187 (89.0)	
Age (mean ± SD)	61 ± 10	61 ± 10	0.535
Age group			
-39	1 (20.0)	4 (80.0)	
40-49	3 (5.5)	52 (94.5)	
50-59	18 (13.3)	117 (86.7)	0.535
60-69	17 (13.6)	108 (86.4)	
70-	12 (11.2)	95 (88.8)	
Examination date			
~2015/08/31	25 (15.2)	140 (84.8)	0.105
2015/09/01~	26 (9.9)	236 (90.1)	
Laboratory data (mean ± SD)			
AST (IU/L)	65.9 ± 43.2	64.8 ± 42.6	0.855
ALT (IU/L)	51.8 ± 45.7	47.0 ± 45.8	0.485
Total bilirubin (mg/dL)	0.9 ± 0.4	0.9 ± 0.6	0.617
Platelet ($\times 10^3/mm^3/\mu L$)	145.4 ± 66.0	151.7 ± 64.4	0.522
HCV RNA ($\times 10^6$/IU/mL)	2.3 ± 3.7	2.2 ± 2.4	0.763
Liver disease			
chronic hepatitis	23 (11.3)	181 (88.7)	
compensated LC	26 (12.5)	182 (87.5)	0.916
decompensated LC	2 (13.3)	13 (86.7)	
HCC			
no	39 (11.0)	316 (89.0)	0.175
yes	12 (16.7)	60 (83.3)	
Past treatment			
naïve	32 (12.0)	235 (88.0)	0.973
experience	19 (11.9)	141 (88.1)	
Past treatment response			
intolerance	3 (12.5)	21 (87.5)	
null response	2 (5.1)	37 (94.9)	0.678
partial response	2 (15.4)	11 (84.6)	
relapse	12 (14.3)	72 (85.7)	

presented so differently according to NS5A polymorphisms and prevalence of drug-resistant variants before treatment is not well known yet in the Koran population.

Methods: To detect HCV variants resistant to NS5A inhibitor in patients with genotype 1b chronic hepatitis C and investigate clinical features with or without drug-resistant variants, amplification and direct sequencing of the HCV NS5A region was carried out on the 427 genotype 1b chronic hepatitis C patients from multi-center cohort, who had not received direct-acting antivirals before.

Results: Amino-acid substitutions for resistance (L31 and/or Y93) were detected in 51 of the 427 (11.4 %) patients, and Y93 (8.7 %) predominated over L31 (2.9 %). However, baseline clinical characteristics and response to previous interferon based treatment were not different according to the existence of drug-resistant variants.

Conclusions: Mutations associated with resistance to NS5A inhibitor were not uncommon in our study population. But drug-resistant variants did not affect clinical features. So it would be important to monitor the baseline variants before the combination therapy of daclatasvir and asunaprevir for genotype 1b chronic hepatitis C.

Keywords: Hepatitis C virus, Genotype 1b, Daclatasvir and asunaprevir, Resistance-associated variants

O-018

Effect of Renal Impairment on HCV Direct Acting Antivirals Drugs (DAA) Primarily Eliminated by Metabolism or Biliary Excretion

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Aims: Renal impairment (RI) can lead to alterations in non-renal (NR) clearance of drugs by affecting drug-metabolizing enzymes and transporters, even if primarily eliminated by NR pathways.

Methods: The effect of RI on HCV DAAs and the impact of study design on dosing recommendations were evaluated. A literature review to assess the impact of RI on drugs primarily eliminated NR vs. those primarily renally cleared identified 75 drugs (27 primarily eliminated by renal clearance, 38 by metabolism/ transport and 10 by mixed mechanisms).

Results: Seven recently developed DAAs, evaluated the effect of RI using a full RI study design (entire range of renal function); four used a reduced design (only subjects with severe RI or end stage renal disease [ESRD]).

For DCV and ASV, a reduced design in ESRD subjects on hemodialysis indicated only small differences in total exposure between controls and ESRD, while a full design for DCV in RI patients demonstrated a 51% increase in unbound AUC(INF), although neither case warrant a dose adjustment. A study of DCV+ASV+ beclabuvir demonstrated 99% and 2.3-fold increases in ASV AUC(TAU) in moderate and severe RI, respectively, demonstrating a need for dose adjustment in severe RI subjects unlike ESRD subjects on hemodialysis.

Literature review indicated that for majority (22/27) of drugs with significant component of renal elimination, Sponsors used a full RI study design. Dosage adjustment in RI subjects was frequently recommended. Full studies were conducted in 68% of drugs eliminated NR. In almost all cases with full RI studies, RI resulted in altered PK; dose adjustments were recommended in 13/38 (34%) cases.

Conclusions: Literature review and in-house BMS results indicate that subjects with RI can have significantly higher exposures of drugs with elimination primarily via metabolism or via transporter-mediated pathways; Sponsors should carefully consider subgroups included in a reduced study design.

Keywords: DAA, HCV, Renal impairment

O-019

High Sustained Virologic Response with Daclatasvir plus Asunaprevir in HCV GT-1b Chinese, Korean and Taiwanese without Baseline NS5A Polymorphisms

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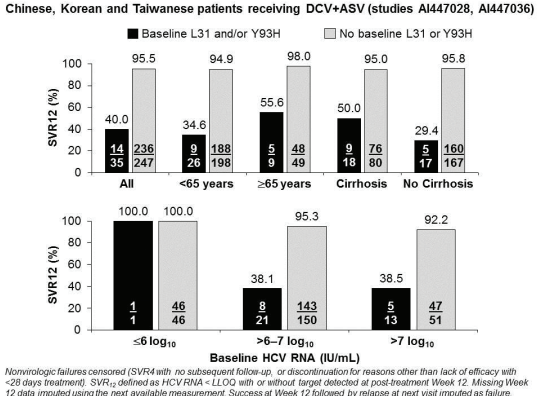
Aims: Daclatasvir (DCV) plus asunaprevir (ASV) has demonstrated high sustained virologic response (SVR) in HCV genotype (GT-)1b infection. NS5A-Y93H and NS5A-L31 resistance-associated polymorphisms (RAPs) to DCV are known to impact DCV+ASV response in GT-1b-infected Japanese. The effect of RAPs on SVR at posttreatment week 12 (SVR12) to DCV+ASV was explored in mainland Chinese, Korean, and Taiwanese.

Methods: Pooled data from 2 studies of DCV (60 mg daily) + ASV (100 mg capsule, twice-daily) for 24 weeks in GT-1b-infected interferon/ribavirin-naive and -experienced patients from mainland China, Korea, and Taiwan. Similar Japanese data (4 studies; n=445) were pooled for comparison. SVR12 with versus without baseline Y93H and/or L31 RAPs was compared by age (<65 vs ≥65 years), cirrhosis status, and baseline HCV-RNA.

Results: SVR12 and baseline NS5A sequences were available for 282 patients (126 mainland Chinese [45%], 80 Koreans [28%], 76 Taiwanese [27%]). NS5A-Y93H and/or -L31 RAPs were observed pretreatment in 8% mainland Chinese, 14% Korean, and 18% Taiwanese patients, compared with 19% in Japanese. SVR12 in all non-Japanese patients is shown (Figure); rates were broadly similar between countries and with Japanese data (Japanese: 96% overall without RAPs, 41% with RAPs). Responses were lower among patients with baseline RAPs. By contrast, SVR12 in patients without RAPs was high (92-100%), irrespective of cirrhosis, age, or baseline HCV-RNA.

Conclusions: At least 95% of HCV GT-1b-infected patients from mainland China, Korea or Taiwan without baseline NS5A-Y93H or -L31 polymorphisms who had HCV-RNA ≤7 log10 IU/mL achieved SVR12 on DCV+ASV, regardless of cirrhosis status and age.



Keywords: SVR, HCV genotype-1b, NS5A polymorphisms, Daclatasvir, Asunaprevir, Chinese, Koreans, Taiwanese

O - 020

Absence of HBV Reactivation among HCV Infected Patients with Reactive Hepatitis B Core Antibody Treated with Ledipasvir/Sofosbuvir for 12 Weeks

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Aims: HBV reactivation during HCV treatment with direct-acting antiviral regimens has been reported in HCV infected patients who are HB surface antigen (HBsAg) negative, HB core antibody (HBcAb) positive, and HBV DNA undetectable. To evaluate the risk of HBV reactivation in these HCV infected patients, we analyzed samples from a Phase 3b study, GS-US-337-0131, of ledipasvir/sofosbuvir (LDV/SOF) for 12 weeks conducted in Korea and Taiwan where HBV is endemic. All enrolled subjects were HBsAg negative at screening per protocol. The SVR12 rate was 98% in this trial.

Methods: A serum sample per patient, collected during post-treatment follow up was analyzed for HBcAb. Samples positive for HBcAb were analyzed for HBV DNA and retested for HBsAg if HBV DNA was detectable.

Results: 173 of 178 patients had one post-treatment sample within the 1 year stability limit. Of the 173 patients, 60% (n=103) were HBcAb positive and HBsAg negative; no subject was HBsAg positive. Two of 103 patients had HBV DNA <20 IU/mL, detected and the remaining patients were <20 IU/mL, target not detected. Median ALT during treatment and post-treatment follow-up were similar between HBcAb positive and negative patients; all patients had ALT declined from baseline. No patients had clinical signs of HBV reactivation during treatment or post-treatment follow up. No differences in overall adverse events or laboratory abnormality observed in patients who were HBcAb positive or negative.

Conclusions: Among 103 HCV-infected patients with reactive HB core antibody and absent HB surface antigen, there was no evidence of HBV reactivation following successful HCV treatment with LDV/SOF. These data suggest HBV reactivation in patients with HCV and reactive HB core antibody is uncommon. A Phase 3b study evaluating 12 weeks of LDV/SOF in patients with chronic HCV and overt HBV (HBsAg positive) co-infection is ongoing in Taiwan and can provide further safety information.

Keywords: Ledipasvir, Sofosbuvir, HBcAb

3. NAFLD, Clinical

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O - 021

Prospective Comparison and Subgroup Analysis of Noninvasive Fibrosis Assessment to Predict Advanced Fibrosis or Cirrhosis in Non-alcoholic Fatty Liver Disease

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Aims: Non-alcoholic fatty liver disease (NAFLD) is currently the most common form of chronic liver disease. Its prevalence continues to rise, and it threatens to become a serious health problem. This study aimed to evaluate the diagnostic accuracy of noninvasive fibrosis assessment in predicting advanced fibrosis or cirrhosis in patients with NAFLD and to identify the clinical factors associated with liver stiffness measurement (LSM).

Methods: Three hundred fifteen patients with a liver biopsy-confirmed diagnosis of NAFLD were prospectively evaluated between January 2013 and December 2015. LSM was performed by acoustic radiation force impulse (ARFI) elastography in all patients. Aspartate aminotransferase to alanine aminotransferase ratio (AAR), FIB-4 index, aspartate aminotransferase to platelet ratio index (APRI), NAFLD fibrosis score (NFS) and BARD score were calculated according to published algorithms. In order to predict advanced fibrosis or cirrhosis, diagnostic measurements of serum fibrosis indices and ARFI imaging were compared by analyzing the area under the receiver operating characteristic (AUROC) curve. Moreover, subgroup analysis was performed for identifying influence clinical factors to predict advanced fibrosis of ARFI elastography.

Results: The median age of the study population was 55 years (range, 18-78). The AAR, APRI, FIB-4 index, NAFLD fibrosis score, BARD score and LSM showed significant, positive correlations with the Kleiner classification (P<0.001). For predicting advanced fibrosis (≥F3), the FIB-4 index was shown the better AUROC (0.866; 95% CI, 0.811-0.922) than ARFI elastography (0.861; 95% CI, 0.8-0.922). The LSM by ARFI had the better AUROC (0.894; 95% CI, 0.827-0.961) than FIB-4 index (0.891; 95% CI, 0.827-0.955) for predicting cirrhosis (F4) (0.894; 95% CI, 0.827-0.961). More severe severity of steatosis by ultrasonography (US), the AUROC value was decreasing of FIB-4 index, APRI and BARD except LSM by ARFI elastography in predicting advanced fibrosis.

Conclusions: LSM by ARFI was a useful noninvasive assessment for predicting advanced fibrosis and cirrhosis in patients with NAFLD. In addition, the FIB-4 index exhibited acceptable diagnostic performance in the assessment of hepatic fibrosis in patients with NAFLD. The clinical factors such as obesity, diabetes and severity of steatosis influenced on the noninvasive serum fibrosis indices. But diagnostic performance of ARFI elastography was not affected from clinical factors. Therefore, LSM by ARFI is the best assessment for diagnosis of advanced fibrosis.

Keywords: Acoustic radiation force impulse, Liver stiffness, Fibrosis, Non-alcoholic fatty liver disease

O - 022

The Accuracy of Transient Elastography and Comparison of Non-invasive Markers for Assessing Fibrosis in Korean Patients with Nonalcoholic Fatty Liver Disease

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Aims: The prevalence of nonalcoholic fatty liver disease (NAFLD) is growing worldwide. We investigated whether liver stiffness (LS) and controlled attenuation parameter (CAP), assessed using transient elastography (TE), could assess liver steatosis and fibrosis accurately.

Methods: In a total, 214 patients who underwent liver biopsy and concomitant TE were recruited from a tertiary hospital in Korea and finally analyzed between November 2011 and December 2014. We assessed liver fibrosis using APRI, NAFLD fibrosis score, and FIB-4.

Results: The study population included control group (n=103) and NAFLD group (n=111) according to the results of liver biopsy. Patients with NAFLD exhibited a mean age of 39.7 years and male predominance (n=85, 76.6%). The accuracy of CAP in detecting ≥S1, ≥S2, and ≥S3, assessed by the area under the receiver operating curve (AUROC), were 0.882, 0.906, and 0.870, respectively. The optimal cut-off values for steatosis were 248 dB/m for S1, 281 dB/m for S2, and 315 dB/m for S3. Also, the AUROC of LS in detecting ≥F2, ≥F3, and ≥F4 were 0.887, 0.958, and 0.986, respectively. The optimal cut-off values for fibrosis in patients with NAFLD were 7.65 dB/m for F2, 8.75 dB/m for F3, and 14.45 dB/m for F4. The sensitivity and specificity of the optimal cut-off for detecting ≥F3 and F4 were good (100 and 72% vs. 80.0 and 98.0%), as well as better than other noninvasive markers such as APRI, NAFLD fibrosis score and FIB-4. About 24 (21.6%) patients with NAFLD showed discordance between TE and histology. The predictive factors for discordance were age, body mass index (BMI), and the grade of steatosis.

Conclusions: TE showed the accurate detection of not only steatosis but also fibrosis in patients with NAFLD. In addition, TE showed better sensitivity and specificity for detecting advanced fibrosis and cirrhosis than other noninvasive markers.

Keywords: Fibrosis, Controlled attenuation parameter, Nonalcoholic fatty liver disease, Noninvasive marker

O - 023

Assessment of Change of Intrahepatic Fat Amount Using Controlled Attenuation Parameter in Clinical Trial

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Aims: Multi-echo modified Dixon (mDixon) sequence (MR-PDFF) is a safe and non-invasive alternative for the quantification of hepatic fat content. And it has accepted reasonable method to assess the change of hepatic fat amount in phase II study. Recently controlled attenuation parameter (CAP) has been showed good correlation with intrahepatic fat amount compare to liver biopsy as well as MRS data

in large cross sectional cohort. However there is little known whether change of CAP scores can be used in clinical trial. We investigated the correlation with CAP and MRS by serial examination in clinical trial setting.

Methods: Sixty-five NAFLD patients were evaluated with MRS and transient elastography including CAP in clinical study. Both MRS and CAP were evaluated after three month probiotic clinical trial in patients with NAFLD.

Results: Baseline CAP and MR-PDFF showed good correlation assessing hepatic steatosis (r=0.60, p<0.001). Also, changes of CAP value was also correlated with changes of intra-hepatic fat % using MR-PDFF (r=0.35, p=0.008) in clinical trial setting. Concordance rate of improvement or aggravation was comparable in both two methods. However, the less change amount was small in CAP value, the less concordance rate showed more weak with MR-PDFF. When the change of CAP value after treatment was less than 20, concordance rate with MR-PDFF was decreased to 15/25 (60%).

Conclusions: CAP and MRS have a comparable diagnostic value for the hepatic steatosis quantification as well as assessing changes of hepatic fat amount in clinical trial. However, a careful interpretation of the steatosis change using CAP score should be given when the absolute change value was less than 20 in clinical trial setting.

Keywords: Controlled attenuation parameter, Hepatic steatosis

O - 024

Relationship between Appendicular Sarcopenia and Non-alcoholic Fatty Liver Disease in Korean Population

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Aims: Non-alcoholic fatty liver disease (NAFLD) is characterized by an accumulation of fat droplets in the hepatocyte, which is one of the major causes of liver disease worldwide. Previous studies have shown that NAFLD and sarcopenia and visceral adiposity seem to share similar pathophysiological mechanisms. However, the functional roles of skeletal muscle and visceral adipose tissue in NAFLD have not been elucidated. The aim of this study was to determine whether the skeletal muscle mass affects the progression of NAFLD.

Methods: In the prospective cohort study, we recruited 223 patients with biopsy-proven NAFLD and collected their anthropometric data between January 2013 and August 2015. We performed abdominal fat-amount computed tomography to quantify the visceral and subcutaneous abdominal adipose tissue amount and underwent bioelectrical impedance analysis to measure body fat and muscle composition. Sarcopenia was defined as an appendicular skeletal muscle mass % (ASM%) = [total appendicular skeletal muscle mass (kg) / body weight (kg) × 100].

Results: A total of 223 subjects were analyzed. The mean age was 52.24 ± 14.87 years, and 53.4% of the subjects were men. Men were significantly younger (46.61 ± 14.79 years in men and 58.68 ± 12.14 years in women, P <0.001) and had higher muscle mass than women (31.96 ± 5.16 kg in men and 21.76 ± 2.85 kg in women, P <0.001). In male group, subjects with advanced fibrosis (≥F3) showed significantly higher body mass index (BMI; P =0.006), total body fat mass (P <0.001), and total abdominal adipose tissue (TAT) amount (P =0.016), but lower ASMI (P<0.001) compare to without advanced fibrosis. Meanwhile, there were no significant differences in BMI, total body fat mass, TAT amount, and ASMI between women NAFLD subjects with advanced fibrosis and without.

Conclusions: Appendicular sarcopenia may play a role in fibrosis progression in NAFLD. However, the gender-specific difference in the impact of sarcopenia on NAFLD may be attributed to the interaction among environmental, genetic, and hormonal factors. Therefore, further studies are needed to reveal the causal relationship between appendicular sarcopenia and liver fibrosis in subjects with NAFLD, especially according to gender.

Keywords: Non-alcoholic fatty liver disease, Fibrosis, Sarcopenia

O - 025

Computer-aided Relative Scoring of Fatty Liver Intensity in High Frequency 9 MHz Ultrasound Image: A Feasibility Study

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Aims: Fatty liver (hepatic steatosis) is prevalent in population, who is predisposed to the metabolic syndrome. Because approximately 10% of the cases progress to steatohepatitis (NASH) accompanied by fibrosis, timely diagnosis and management are important. Liver biopsy is the gold standard to measure the severity of steatosis and fibrosis, but its use is not in general. Ultrasonography (US) conventionally using low frequency (3-4 MHz) is qualitatively defined for screening moderate-to-severe steatosis. It is unable to compare hepatic steatosis quantitatively. In this study, we developed a custom-designed algorithm that calculates a relative scoring the fatty liver intensity based on the high frequency 9 MHz B-mode image (HF-9) obtained by US (GE LogiQ-E9), and tested its feasibility.

Methods: Three regions of interest (ROI) with 70x70 pixel size were arbitrarily selected in the HF-9 according to the depth from the surface. Histogram data in each ROI was obtained by Image-J, including mean, standard deviation (SD), skewness and kurtosis of 8-bits grey pixel intensity. Relative intensity score (RIS) in each ROI was determined by the z-score rank. Three RIS were classified by the k-means clustering (k-MC) and principal component analysis (PCA), and finally an algorithm was established to estimate the fatty grade reflecting fat content of liver tissue. The program was developed to be automatically calculated on MS access database. We used liver biopsy specimens with various degrees of fat content as reference.

Results: A total of 759 subjects were included, consisting of 65 cases to build-up the model and simulation (Group-MS) and 684 cases to test algorithm (Group-T). PCA suggested that the mean was more significant for making category groups than other parameters. The skewness and kurtosis were helpful for differentiating the presence of fatty liver, regardless of the fibrosis degree. The k-MC showed that six different clustering might be possible by the combination patterns of the mean pixel intensity of three ROI. Based on the data

from group-MS, we classified six groups representing the fat-content severity (0 to 5). Diagnostic reliability for the moderate-to-severe fatty liver was comparable to that of the 3 MHz inspection (AUC = 0.9023, 95% CI: 0.8787-0.9258). HF-9 analysis was more useful for detecting the mild-to-moderate grade steatosis and serial comparison than the conventional US.

Conclusions: Computer-aided relative scoring of pixel intensity measured in high frequency 9 MHz US image is reliable for estimate fatty liver grade, and is feasible for the clinical application.

Keywords: Ultrasonography, Fatty liver, Steatohepatitis, Elasticity Imaging techniques

O - 026

The Impact of Controlled Attenuation Parameter on Liver Stiffness Measurement Using Transient Elastography in Patients with Non-alcoholic 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: Two hundred eleven subjects with biopsy-proven NAFLD were included in this prospective analysis. All patients underwent acoustic radiation force impulse elastography (ARFI) and 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 advanced fibrosis (≥F3) and cirrhosis.

Results: For diagnosing advanced fibrosis, the AUROCs for TE (CAP-adjusted E) were 0.889 (optimal cut-off, -7.739; sensitivity [se], 85.37%; and specificity [sp], 87.06%) by log odds and 0.883 (optimal cut-off, 0.263; se, 82.93%; sp, 91.76%) by formula calculated using discriminant function analysis, while, for diagnosing cirrhosis, those for TE (CAP-adjusted E) were 0.903 (optimal cut-off, -5.177; se, 90.91%; sp, 88.36%) by log odds and 0.904 (optimal cut-off, 0.381; se, 90.91%; sp, 88.36%) by formula calculated using discriminant function analysis. The AUROCs (for ≥F3, 0.893 and for F4, 0.915) for TE (E) were not significantly different from those for TE (CAP-adjusted E). However, specificity (for ≥F3, 52.94%; for F4, 84.66% in TE) was markedly improved after adjustment for CAP without diminishment of sensitivity (for ≥F3, 85.37%; for F4, 90.91% in TE) at the optimal cut-off values.

Conclusions: There was a significant positive correlation between CAP-adjusted E and fibrosis stages in subjects with NAFLD. Although CAP-adjusted E was not superior to E in diagnosing advanced fibrosis and cirrhosis, measurement of CAP-adjusted E might obviate the need for liver biopsy in those with NAFLD.

Keywords: Sonoelastography, Pathology, Steatohepatitis, Liver cirrhosis

O - 027

Risk of Hepatocellular Carcinoma in Korean Patients with Metabolic Syndrome: A Big Data Analysis

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Aims: The Metabolic syndrome (MetS) and/or its individual components have been linked to the development of various cancers. Recent studies have suggested MetS as a risk factor of hepatocellular carcinoma (HCC). However, the association between MetS and HCC is in controversial especially in an HBV- and HCV-endemic area. We evaluated the association between the MetS and HCC in Korea.

Methods: The HCC incidences according to the MetS were analyzed in general population by using the Health Examination Cohort data of National Health Insurance. We followed all 112,794 people who were 40-79 years old and had health examination in 2002 or 2003. According to limited source justification, the criteria for MetS are as follows: BMI 25+, hypertension SBP 130+ or DBP 85+, fasting blood glucose (FBG) 100mg/dL+ and total cholesterol (TC) 240 mg/dL+. Cox proportional hazard regression models were used.

Results: Out of 112,794 people, 40,443(35.9%) had one, 26,410(23.4%) had two, 19,874(17.6%) had three, and 1,604(1.4%) had four components of MetS. HCC incidence rates for 10 years were 1.27% for one, 1.38% for two, 0.59% for three, and 1.12% for four components groups of MetS. Univariate analysis on risk of HCC showed significant results with hypertension (HR: 1.184), FBG (HR: 1.256) and TC (HR: 0.676). However, after adjusting for age, sex, alcohol drinking, and viral hepatitis (B and/or C), only TC (HR: 0.717) showed a significant result. After excluding TC which showed protective effect, adjusted HRs of BMI, FBG, and hypertension were not significant (1.016, 1.046 and 1.038, respectively).

Conclusions: MetS may not be a significant risk for HCC development in a Korean population-based study. A subsequent analysis of the HCC risk and MetS is currently under way in the second set including data of triglyceride and HDL-cholesterol.

Keywords: Cohort, Hepatocellular Carcinoma, Metabolic syndrome, Risk factor

O - 028

Noninvasive Fibrosis Markers are Associated with Coronary Artery Calcification in Nonalcoholic Fatty Liver Disease

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Aims: Nonalcoholic fatty liver disease (NAFLD) is associated with increased risk of coronary artery disease. In addition, the advanced fibrosis in NAFLD patients is associated with cardiovascular disease

and overall mortality. Therefore, we investigated the association between coronary atherosclerosis and noninvasive fibrosis markers to detect the high risk population for coronary artery disease.

Methods: Between January 2011 and December 2015, a total 665 subjects with NAFLD were analyzed. NAFLD was diagnosed by ultrasonography in St. Vincent's Hospital Heath Promotion Center. Coronary atherosclerosis, represented as coronary artery calcification score (CACS), was assessed by cardiac computed tomography. NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) score, aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) score, and Forns index were used as noninvasive fibrosis markers.

Results: The mean age of the study population was 51.5±9.3 years, and 486 subjects (73.5%) were male. On univariate analysis, high CACS (≥ 100) was significantly associated with old age (≥ 55 years), diabetes mellitus, serum glucose (≥100mg/dL), and estimated glomerular filtration rate (GFR) (all Ps < 0.05), and seemed to be associated with hypertension and body mass index (≥ 25kg/m^2) (all Ps < 0.10). On multivariate analysis, old age and male gender were only significant risk factors (P < 0.001 and P = 0.024). NFS, FIB-4 and Forns index were significantly associated with high CACS (all Ps < 0.001) and NFS and FIB-4 score were significantly factors even after adjustment for traditional risk factors (P = 0.043 and P = 0.009). AUROCs of NFS and FIB-4 were 0.689 and 0.683 for predicting the high CACS, and the cut-off values were -1.774 and 0.85, respectively.

Conclusions: Hepatic fibrosis assessed by noninvasive fibrosis markers, such as NFS and FIB-4, was independently with high CACS. Therefore, noninvasive fibrosis markers are helpful to detect the high risk population of coronary artery disease.

Keywords: Nonalcoholic fatty liver disease, Coronary artery disease, Noninvasive, Fibrosis

O - 029

Nonalcoholic Fatty Liver Disease and Progression of Coronary Artery Calcification: A Cohort Study

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Aims: Nonalcoholic fatty liver disease (NAFLD), a hepatic manifestation of the metabolic syndrome, was associated with subclinical atherosclerosis in many crosssectional studies, but the prospective association between NAFLD and the progression of atherosclerosis has not been evaluated. This study was conducted to evaluate the association between NAFLD and the progression of coronary atherosclerosis.

Methods: This cohort study included 4,731 adult men and women with no history of CVD, liver disease or cancer at baseline who participated in a repeated regular health screening exam between 2004 and 2013. Fatty liver was diagnosed by ultrasound based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation and bright vessel walls. Progression of coronary artery calcium (CAC) scores was measured using multidetector CT scanners.

Results: The annual rate of CAC progression in participants with and without NAFLD were 22% (95% confidence interval 20 - 23%) and 17% (16 - 18%), respectively (p<0.001). The multivariable ratio of progression rates comparing participants with NAFLD to those without NAFLD was 1.04 (1.02 - 1.05; p<0.001). The association between NAFLD and CAC progression was similar in most subgroups analyzed, including in participants with CAC 0 and in those with CAC > 0 at baseline.

Conclusions: In this large cohort study of adult men and women with no history of CVD, NAFLD was significantly associated with the development of CAC independently of cardiovascular and metabolic risk factors. NAFLD may play a pathophysiologic role in atherosclerosis development and may be useful to identify subjects with a higher risk of subclinical disease progression.

Keywords: Cardiovascular disease, Fatty liver, Ultrasonography

4. HBV, Clinical

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O - 030

A Phase 3 Study of Tenofovir Alafenamide Compared with Tenofovir Disoproxil Fumarate in Patients with HBeAg-positive Chronic Hepatitis B

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Table. Efficacy and Safety at Week 48

n/N (%)	TAF (N=581)	TDF (N=292)	P value
HBV DNA <29 IU/mL	371/581 (63.9)	195/292 (66.8)	0.25
ALTnormalization(centrallaboratory)[a]	384/537 (71.5)	179/268 (66.8)	0.18
ALT normalization (AASLD criteria)[b]	257/572 (44.9)	105/290 (36.2)	0.014
HBsAg seroconversion	3/576 (0.5)	0	0.22
HBeAg seroconversion	58/565 (10)	23/285 (8)	0.32
Hip BMD, mean (SD) % change (g/cm^2)	-0.10 (2.29)	-1.72 (2.57)	<0.001
Spine BMD, mean (SD) % change (g/cm^2)	-0.42 (2.93)	-2.29 (3.13)	<0.001
sCr, mean (SD) change (mg/dL)[c]	0.01 (0.12)	0.03 (0.10)	0.020
Proteinuria (dipstick) %	158/577 (27.4)	65/286 (22.6)	0.21
$eGFR_{CG}$, mean(SD)change(mL/min)[d]	-0.3 (14.5)	-4.7 (13.5)	<0.001

Efficacy results are missing = failure
[a]ULN 43 U/L males, 34 U/L females; [b]ULN30U/Lmales,19U/Lfemales;[c]sCrisserumcreatinine; [d]eGFRCGisCLCr(Cockcroft-Gault)

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Aims: Tenofovir alafenamide (TAF), a novel prodrug of tenofovir (TFV), is more stable in plasma and enhances delivery of TFV into hepatocytes while lowering circulating levels of TFV by approximately 90% compared to tenofovir disoproxil fumarate (TDF).
Methods: In this Phase 3 study, patients with HBeAg-positive chronic hepatitis B (CHB) were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD and treated for 96 weeks. After Week 96, patients receive open label TAF for 48 weeks. The primary efficacy analysis was the percent of patients with HBV DNA <29 IU/mL at Week 48. Key secondary safety endpoints were assessed sequentially: changes in hip and spine bone mineral density (BMD), changes in serum creatinine (sCr), and dipstick proteinuria. Markers of bone formation and resorption, and renal tubular function were also assessed.
Results: 873 patients were randomized and treated at 164 sites in 19 countries. Baseline characteristics included: mean age 38 years, 83% males, 82% Asians; 47% had HBV DNA ≥ 8 log10 IU/mL, and 26% were treated previously with nucleos(t)ides. At Week 48, TAF was non-inferior in efficacy to TDF with virologic response rates of 63.9% with TAF and 66.8% with TDF. A greater percentage of patients treated with TAF achieved normalization of serum ALT values. Patients on TAF experienced significantly less declines in hip and spine BMD, and a smaller increase in sCr than TDF; eGFRCG, and renal tubular markers also changed less with TAF. No viral resistance was observed in 22/581 (3.8%) and 11/292 (3.8%) of TAF and TDF patients, respectively, who qualified for testing.
Conclusions: Compared to TDF 300 mg, the efficacy of TAF 25 mg in patients with HBeAg-positive CHB was noninferior. Safety was also improved, with less change in bone and renal parameters.
Keywords: Tenofovir Alafenamide, Tenofovir Disoproxil Fumarate, HBeAg-positive, Phase 3

O - 031

D2AS Score Predicts Development of Hepatocellular Carcinoma in Chronic Hepatitis B Who Are Outside the Current Treatment Recommendations

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Aims: As antiviral therapy for chronic hepatitis B (CHB) reduces the risk of hepatocellular carcinoma (HCC), ideally, no HCC should develop in those who are not recommended for therapy. Yet, HCC development who were outside of current treatment recommendation has been reported.
Methods: A simple HCC risk score was developed from 971 patients with CHB with elevated HBV DNA levels who were outside the current treatment criteria due to having normal or mildly elevated alanine aminotransferase (ALT) levels (of whom 26 patients developed HCC during follow-up). Variables included in the risk score were serum HBV DNA level (used twice), age, and sex (D 2AS score). The score was validated from an independent cohort of 507 patients (of whom 15 patients developed HCC).
Results: A 4-point risk scale was developed, with HCC risk ranging from 0-29.1% at 5 years for the lowest and highest D 2AS score. The D 2AS score had the highest area under receiver operating curves (AUROCs) for predicting development of HCC at 3/5 years (0.895/0.884), compared with that of risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) (0.814/0.812) and Fibrosis-4 (FIB-4) (0.759/0.702) scores, age (0.739/0.718), and ALT (0.666/0.766) and HBV DNA (0.559/0.556) levels. The calculated AUROCs to predict development of HCC at 3/5 years were 0.889 (95% confidence interval [CI] 0.796-0.983)/0.876 (95% CI, 0.789-0.963) in the validation cohort, with 5-year HCC incidence rates of 0%, 0.6%, 6.3%, and 19.2% for very low, low, high, and very high D 2AS scores, respectively.
Conclusions: HCC developed in patients with elevated HBV DNA levels and normal or mildly increased ALT levels. The D2AS risk score can play a valuable role in risk stratification, and may be useful to guide clinical decisions for enhanced surveillance or treatment to reduce HCC risk in this population.
Keywords: Hepatocellular carcinoma, Risk score, Hepatitis B

O - 032

A Randomized Trial Evaluating the Antiviral Efficacy of Switching from Lamivudine plus Adefovir to Tenofovir Monotherapy in Lamivudine-resistant Chronic Hepatitis B Patients with Undetectable Hepatitis B Virus DNA

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Aims: Tenofovir (TDF) monotherapy is a standard treatment for patients who have lamivudine (LAM)-resistant chronic hepatitis B (CHB). However, the efficacy of switching to TDF monotherapy for LAM resistant CHB patient with undetectable HBV DNA while on LAM plus adefovir (ADV) combination therapy (stable switching) is not clear.

Methods: In this non-inferiority trial, LAM-resistant CHB patients who had undetectable serum HBV DNA (<20 IU/mL) for more than 6 months after initiating LAM plus ADV combination therapy were randomized (in a 1:2 ratio) to continue LAM plus ADV combination therapy (LAM/ADV group, n=58) or TDF monotherapy (TDF group, n=111) and followed-up with serum biochemistry and HBV DNA in 12 week intervals for 96 weeks. The primary endpoint of this study was the proportion of patients with viral reactivation at week 96. Viral reactivation was defined as HBV DNA >40 IU/mL at two consecutive timepoints, or persistent HBV DNA levels of 20-40 IU/mL at three consecutive timepoints.

Results: A total of 169 CHB patients were enrolled in this study including 74 with compensated cirrhosis. There were no significant differences between two groups in age, gender, biochemistry findings and duration of LAM and ADV combination therapy at baseline. Twelve (20.7%) patients in the LAM/ADV group and 18 (16.2%) patients in TDF group were HBeAg-positive. Nine patients (4 in the LAM/ADV group and 5 in the TDF group) discontinued the study. After a mean follow up period of 96 weeks, there was no subject in either group experienced viral reactivation in both groups. One patient achieved HBsAg seroconversion in TDF group (1/106, 0.94%). The number of patients with HBeAg loss at week 96 was 5/12(41.7%) and 3/17(17.6%) in the LAM/ADV and TDF groups, respectively. Two patients (2/17, 11.8%) achieved HBeAg seroconversion in TDF group. Transient virological rebound occurred in 14 patients (6 patients in LAM/ADF group and 8 patients in TDF group) through 96 weeks, but all patients achieved HBV DNA undetectable at the next visit. There were no patients experienced an increase of serum creatinine levels of ≥0.5 mg/dL above baseline.

Conclusions: Stable switching to TDF monotherapy for 96 week showed a comparable virological response to continuous LAM plus ADV combination therapy in LAM resistant CHB patients with undetectable HBV DNA. (Trial registration number Clinicaltrial.gov ID NCT01732367)

Keywords: Chronic hepatitis B, Lamivudine resistance, Tenofovir, Stable switching

O - 033

Switching Tenofovir Disoproxil Fumarate (TDF) plus Entecavir Combination Therapy to TDF Monotherapy Is Safe and Efficacious in Patients with Multiple Drug-resistant Chronic Hepatitis B: Randomized Trial

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Aims: Combination therapy with a nucleoside analogue and a nucleotide analogue has been generally recommended for the treatment of patients harboring multiple drug-resistant (MDR) hepatitis B virus (HBV). Little data are available regarding whether switching the combination therapy to tenofovir disoproxil fumarate (TDF) monotherapy is safe and efficacious in patients with MDR HBV.

Methods: This integrated analysis combines results from two Phase 4 trials for 192 patients with HBV resistant to entecavir and adefovir, respectively. In both studies, patients with serum HBV DNA levels >60 IU/mL were randomized to receive TDF (300 mg/day) monotherapy (n=95) or TDF and entecavir (1 mg/day) combination therapy (TDF+ETV, n=97) for 48 weeks. All who completed 48 weeks in either group received TDF monotherapy for 48 additional weeks.

Results: Mean basal HBV DNA level was 4.08 log10 IU/mL without significant difference between TDF and TDF+ETV groups. All patients had HBV resistance mutations to entecavir and/or adefovir in addition to lamivudine; rtT184A/C/F/G/I/L/S (n=73), rtS202G (n=64), rtM250L/V (n=17), rtA181V/T (n=97), rtN236T (n=39), rtL180M (n=157), and rtM204V/I (n=192). Sixty-eight and 34 patients, respectively, had single (rtA181V/T or rtN236T) and double (rtA181V/T and rtN236T) resistance mutations to adefovir at baseline. The proportion of patients with HBV DNA <15 IU/mL was not significantly different between the TDF and TDF+ETV groups at week 48 (66.3% vs 68.0%; p=0.80). At week 96, HBV DNA was detectable in 63 patients (32.8%), but the level was below 3 log10 IU/mL (1.88±0.46 log10 IU/mL) in 62 patients. None developed additional resistance mutations.None developed additional resistance mutations. After switching TDF+ETV to TDF, virologic breakthrough occurred only in one patient at 96 weeks by poor drug adherence. Only higher HBV DNA level (OR, 0.46; P<0.001) and harboring double adefovir-resistance mutations (OR, 0.16; P=0.003) at baseline were significantly associated with lower rate of virologic response at 96 weeks by multivariable analysis.

Conclusions: In patients with MDR HBV, TDF monotherapy provided a virologic response comparable to that of TDF+ETV combination therapy during 48 weeks of treatment. Switching TDF+ETV combination therapy to TDF monotherapy was safe and efficacious.

Keywords: Tenofovir, Combination therapy, Hepatitis B virus, Resistance

O - 034

Efficacy and Safety of Tenofovir DF (TDF) in Chronic Hepatitis B Patients (CHB) with Lamivudine Resistance (LAM-R): 5-year Results

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Aims: In CHB patients with LAM-R, TDF has shown efficacy comparable to FTC/TDF and no detectable TDF resistance at 2 years. The final 5 year efficacy and safety results from this trial are presented.

Methods: CHB patients on LAM with HBV DNA >3 log10 IU/mL and with documented LAM-R were randomized (1:1) to TDF or FTC/TDF and followed for 5 years.

Results: Two hundred eighty patients were randomized; 232 (83%) completed 5 years of treatment. At baseline, mean age was 47 years, most were male (75%) and non-Asian (66%); 53% were HBeAg negative. Mean HBV DNA was 5.7 log10 IU/mL and 42% had ALT ≤ULN at baseline. At Year 5, virologic, serologic, and biochemical responses were similar among groups, and remained stable. Nine patients (4-TDF, 5-FTC/TDF) discontinued due to an adverse event, including increased serum creatinine in 1 patient. For both groups combined, confirmed renal safety endpoints over 5 years were: CrCL <50 mL/min in 19 (6.8%) patients (12 requiring dose modification), increases in serum creatinine of ≥0.3 and ≥0.5 mg/dL from baseline in 21 (7.5%) and 2 (0.7%) patients, respectively, and serum phosphorus <2 mg/dL in 3 (1.1%) patients. Mean declines in BMD (g/cm2) from baseline for hip and spine BMD, respectively, were 1.7% and 1.5% at Year 2, and 2.5%, and 1% at Year 5. Seven patients experienced fracture (all except 1 were trauma-related). No TDF resistance was detected through 5 years by population sequencing.

Conclusions: In LAM R patients with CHB treated for 5 years with TDF, a high rate of HBV DNA suppression was achieved and maintained with no detectable TDF resistance. There is no apparent advantage of combination FTC/TDF in this population. Renal events associated with TDF occurred in up to 7.5% of patients, and average losses in bone mineral density of 1 2.5% were observed.

Keywords: TDF, LAM-R, Long-term results

Response % (n/N)	TDF (N=141)	FTC/TDF (N=139)
HBV DNA <69 IU/mL	83 (117/141)	83 (115/139)
HBV DNA <29 IU/mL	82 (115/141)	82 (114/139)
Normalized ALT[a]	65 (51/79)	71 (59/83)
HBeAg loss[b]	25 (16/65)	19 (13/68)
HBeAg seroconversion[b]	12 (8/65)	10 (7/68)
HBsAg loss	1 (2/141)	4 (5/139)
HBsAb seroconversion	0	<1 (1/139)

[a]Includes only patients with ALT>ULN at BL; [b]HBeAg+ patients

O - 035

Switching to Tenofovir versus Continuing Entecavir in Chronic Hepatitis B Patients with Partial Virologic Response During Entecavir Therapy: STEEP Study

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Aims: Entecavir has been widely used for treatment-naïve chronic hepatitis B patients. However, about 20% of patients show partial virologic response (PVR) after 2 year of entecavir therapy [Yoon, et al, 2011]. If the HBV DNA continued to be detected, underlying liver disease may progress, and the risk of hepatocellular carcinoma can be increased. Therefore, switching to more potent antiviral therapy may be needed.

In this study, we compared the efficacy of switching to tenofovir with continuing entecavir in patients who shows PVR to entecavir.

Methods: This is an investigator initiated open label randomized controlled trial (NCT01711567). Primary end point was a virologic response rate 12 months (VR, HBV DNA < 20 IU/mL).

We included chronic hepatitis B patients receiving entecavir 0.5 mg more than 12 months with detectable HBV DNA over 60 IU/mL, but no resistance to entecavir.

Results: A total of 45 patients were enrolled. Twenty two patients were randomized to tenofovir and 23 patients to entecavir arm. Baseline characteristics were not significantly different between the groups.

After 12 month of treatment, VR rate were significantly higher in tenofovir group compared with entecavir group by per protocol analysis (55% vs 20%, P = 0.022) as well as intention-to-treat analysis (50% vs 17.4%, P= 0.020). At month 12, the mean HBV DNA level was lower (1.54 vs. 2.01 log IU/mL, P = 0.011) and the degree of HBV DNA reduction was greater (-1.13 vs. -0.67 log IU/mL, P = 0.024) in tenofovir group than entecavir group, respectively. Proportion of patients with normal ALT and HBeAg loss/seroconversion rate were not different between the groups.

Conclusions: In chronic hepatitis B patients with PVR to entecavir, switching to tenofovir would be a better strategy to achieve optimal response.

Keywords: Chronic hepatitis B, Partial virologic response, Tenofovir, Entecavir

O - 036

A Comparison between Transient Elastography and FIB-4 to Assess the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

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Aims: Liver stiffness (LS), assessed using transient elastography (TE), and FIB-4 can both estimate the risk of developing hepatocellular carcinoma (HCC). We compared prognostic performances of LS and FIB-4 to predict HCC development in patients with chronic hepatitis B (CHB).

Methods: Data from 1,308 patients with CHB, who underwent TE, were retrospectively analyzed. FIB-4 was calculated for all patients. The cumulative rate of HCC development was assessed using Kaplan-Meier curves. The predictive performances of LS and FIB-4 were evaluated using time-dependent receiver-operating characteristic (ROC) curves. The differences in the areas under the ROC curves (AUROCs) between LS and FIB-4 models were tested using a bootstrap resampling method.

Results: The mean age (883 men) was 50 years. During follow-up (median 6.1 years), 119 patients developed HCC. The AUROCs predicting HCC risk at 3, 5, and 7 years were consistently greater for LS than for FIB-4 (0.791~0.807 vs. 0.691~0.725; all P<0.05). Similarly, when the respective AUROCs for LS and FIB-4 at every time point during the 7-year follow-up were plotted, LS also showed consistently better performances than FIB-4 after 1 year of enrollment. In addition, when LS and FIB-4 were processed as categorical scales using pre-defined cutoffs [<8 kPa, 8~13 kPa, 13~18 kPa, 18~23 kPa, and >23 kPa for LS and <1.25, 1.25~1.70, 1.70~24.0, and >2.40 for FIB-4], LS showed significantly better performances than FIB-4 in predicting HCC development within 3 years or 5 years (all P<0.05). The difference was marginal, however, in terms of predicting HCC development within 7 years (P=0.075). The combined use of LS and FIB-4 significantly enhanced prognostic performances compared with the use of FIB-4 alone (P<0.05), but the AUROCs of the combined scores were statistically similar to those of LS alone (P>0.05).

Conclusions: LS showed significantly better performances than FIB-4 in assessing the risk of HCC development. The combined use of LS and FIB-4 did not provide additional benefit compared with the use of LS alone. Hence, LS assessed using TE might be helpful for optimizing HCC surveillance strategies.

Keywords: Chronic hepatitis B, Hepatocellular carcinoma, Liver stiffness, FIB-4

O - 037

Chronic Hepatitis B Infection and Non-hepatocellular Cancers: A Hospital Registry-Based, Case-control Study

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Aims: There have been several reports of the involvement of Hepatitis B virus (HBV) infections in non-hepatocellular carcinogenesis. This prospective hospital registry-based case-control study aimed to investigate the sero-epidemiological association between chronic HBV infection and various types of cancer.

Methods: 95,034 patients with first-diagnosed non-hepatocellular malignancy in a tertiary hospital between 2007 and 2014; and 118,891 non-cancer individuals as controls from a health promotion center were included. Cases and controls were compared for HBV surface antigen (HBsAg) positivity by unconditional and conditional regression with adjustment for age, hypertension, diabetes, body mass index, alcohol consumption, smoking status and cholesterol level in both genders.

Results: An analysis of matched data indicated significant associations of HBV infection with lymphoma (adjusted odds ratio [AOR] 1.53 [95% CI 1.12-2.09] in men and 3.04 [1.92-4.82] in women) and biliary cancer (2.59 [1.98-3.39] in men and 1.71 [1.16-2.51] in women). Cervical (1.49 [1.11-2.00]), uterine (1.69 [1.09-2.61]), breast (1.16 [1.02-1.32]), thyroid (1.49 [1.28-1.74]), and lung cancers (1.79 [1.32-2.44]) in women; and skin cancer (5.33 [1.55-18.30]) in men were also significantly related to HBV infection. There were also possible relationships between positive HBsAg and stomach, head and neck, kidney, and thyroid cancers in men, and colon and brain cancers in women, in multivariable models.

Conclusions: Chronic HBV infection is closely correlated with several malignant disorders including lymphoma, and biliary, cervical, uterine, breast, thyroid, lung, and skin cancers. These findings may offer additional insights into the development of these neoplasms and may suggest the need to consider HBV screening in cancer patients and cancer surveillance in HBV-infected subjects.

Keywords: Hepatitis B virus, Malignancy, Cancer

O - 038

Treatment Efficacy and Safety of Tenofovir-based Therapy in Chronic Hepatitis B Patients for 96 Weeks: A Real Life Cohort Study in Korea

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Aims: We aimed to evaluate the efficacy and safety of Tenofovir disoproxil fumarate (TDF) based therapy in naïve and treatment experienced chronic hepatitis B (CHB) patients for 96 weeks in Korean

real life practice.

Methods: 209 CHB patients who had prescription for TDF at Seoul and Daejeon St. Mary's hospital were enrolled from December, 2012 to October, 2014. We compared the virological responses and renal safety of naive and treatment experienced patients

Results: Overall complete virological response (CVR) showed 80.4% and 84.6% of patients at week 48 and 96, respectively. In subgroup analysis, CVR at week 96 were 88.4%, 75.0 %, 75.5%, and 83.3%, in the lamivudine-resistant (LAM-R) group, Adefovir-resistant (ADV-R) group, multidrug-resistant (MDR) group, and suboptimal response group, respectively. In a multivariate analysis, ADV-R, MDR, HBV DNA, and HBeAg were independent predictors for CVR. In renal safety, Diabetes mellitus (DM), cirrhosis, and initial low estimated glomerular filtration rate were independent factors affecting Cr elevation (≥ 0.5mg/dL). Moreover, we note that 2 patients with DM and cirrhosis have experienced TDF-related Fanconi syndrome.

Conclusions: TDF-based therapy demonstrated sustained viral suppression and a favorable safety throughout 2 years. Compared to the naïve group, the LAM-R and suboptimal response group showed comparable efficacy, while the ADV-R group and MDR group both showed a relatively low efficacy. Also, the ADV-R group and MDR group were significantly associated with a low CVR. Close monitoring of renal function may be recommended in CHB patients receiving TDF, especially with DM and cirrhosis

Keywords: Tenofovir disoproxil fumarate, Chronic hepatitis B, Virological response, Renal safety

5. HCV, Clinical

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O - 039

The Experience of Daclatasvir and Asunaprevir Treatment in Korean Patients with Hepatitis C Genotype 1b Infection

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Aims: Daclatasvir plus asunaprevir (DCV+ASV) has demonstrated potent antiviral activity in patients with hepatitis virus C (HCV) genotype 1b (GT-1b) infection. The use of DCV+ASV was approved by the Korean health insurance last August. We investigated short-term result of DCV+ASV treatment in Korea.

Methods: We analyzed 236 consecutive CHC patients treated with DCV+ASV from August 2015 to December 2015. The patients received DCV (60mg once daily) plus ASV (100mg twice daily) for 24 weeks. End of treatment (EOT), sustained virological response at post-treatment Week 12 (SVR 12) and safety outcomes were evaluated.

Results: The median age was 62.0 (range: 28-86) years, and 107 (45.3%) patients were male. Among 236 patients, 98 (41.5%) patients just completed DCV+ASV treatment. Except for six patients with viral breakthrough, 92 (93.9%) patients achieved EOT. According to treatment group, 94.8% (55/58), 100% (17/17), 100% (12/12) and 72.7% (8/11) patients showed EOT in treatment-naïve, non-responder, relapse, and interferon ineligible/intolerant group, respectively. Three (50%) patients who failed EOT showed baseline NS5A-93H mutation. Cirrhosis and hepatocellular carcinoma (HCC) were identified in 34 (15.5%) and 32 (14.6%) patients, of which 33 (97.1%) and 16 (50%) showed EOT. Among 16 (6.8%) patients with NS5A-93H or NS5A-L31M/V resistance-associated variants (RAVs), 13 (81.3%) patients achieved ETR. With multivariate analysis, NS5A RAVs was identified as an independent predictor for treatment failure in DCV+ASV. The incidence of serious adverse events was 1.4%. Treatment was stopped due to aggravation of renal function, gastrointestinal trouble and increase of ascites.

Conclusions: Dual therapy with DCV+ASV resulted in high EOT rates and well-tolerated in Korean patients with HCV GT-1b infection. Further studies are needed to monitor long-results of DCV+ASV treatment.

Keywords: Daclatasvir, Asunaprevir, Hepatitis C, Genotype 1b

O - 040

High Therapeutic Efficiency of LDV/SOF in Asian Patients with CHC Genotype 1 Infection

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Aims: Current Asian treatment practices for Chronic Hepatitis C (CHC) Genotype (GT) 1 patients use regimens containing pegylated interferon and ribavirin (PR). As interferon-free regimens become the standard of care in most Western countries, it is necessary to understand the potential impact of an all-oral, PR-free single-tablet regimen of Ledipasvir/Sofosbuvir (LDV/SOF) on Asian CHC patients. The aim of this study was to estimate long-term health outcomes of LDV/SOF therapy in 4 Asian countries: Taiwan, South Korea, Singapore, Hong Kong.

Methods: A hypothetical cohort of 10,000 adult patients/country was modeled with a hybrid decision tree and Markov state-transition model capturing the natural history of CHC and treatment implications over a lifetime. Efficacy was based on randomized controlled trials; country-specific demographics, HCV-related epidemiology and treatment data were retrieved from literature. Therapeutic efficiency was

Table 1. Long-Term Health Outcomes of No Treatment vs PegIFN+RBV vs LDV/SOF

	Regimen	Number of new cases in a n=10,000 cohort				
		DCC	HCC	LT	HCV-related deaths	Overall advanced Liver Disease
Taiwan	LDV/SOF 12 wks	73	168	10	203	454
	PR	1,702	1,261	222	1,622	4,808
	No treatment	2,697	1,954	343	2,799	7,792
Korea	LDV/SOF 12 wks	72	163	11	203	449
	PR	2,014	1,491	281	2,197	5,984
	No treatment	3,404	2,479	469	4,113	10,466
Singapore	LDV/SOF 12 wks	69	161	11	203	443
	PR	2,168	1,607	316	2,517	6,608
	No treatment	3,681	2,687	529	4,681	11,578
Hong Kong	LDV/SOF 12 wks	70	163	11	206	449
	PR	2,228	1,651	328	2,621	6,828
	No treatment	3,794	2,770	551	4,887	12,001

defined as the number of advanced liver disease (ALD) cases averted (decompensated cirrhosis, hepatocellular carcinoma, liver transplants, HCV-related deaths) with LDV/SOF relative to PR or no treatment (NT) in treatment-naïve patients. The differing immunomodulatory and anti-tumor effects of the therapies were not modeled.

Results: A 12 week regimen of LDV/SOF compared to PR/NT is estimated to substantially impact CHC disease burden by reducing the incidence of ALD (Table 1): -90.6% / -94.2% vs. PR/NT (Taiwan), -92.5% / -95.7% (South Korea), -93.3% / -96.2% (Singapore), -93.4% / -96.3% (Hong Kong).

Conclusions: LDV/SOF is a highly effective treatment associated with potentially more favorable health outcomes when compared with current treatment practices or no treatment for GT1 CHC Asian patients.

Keywords: LDV/SOF, Asia, Chronic Hepatitis C, Therapeutic Efficiency

O - 041

Clinical Characteristics of HBV/HCV Co-infection Over HCV Mono-infection Based on a Real-life Cohort

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Aims: Hepatitis B virus (HBV)/hepatitis C virus (HCV) co-infection is found approximately 2-10% of chronic hepatitis C (CHC) patients. However, the clinical relevance of HBV/HCV co-infection for disease severity, long term outcomes including hepatocellular carcinoma and treatment efficacy are still under debate. In this study, we evaluated the clinical characteristics and the treatment outcomes of HBV/HCV co-infection in comparison of HCV mono-infection.

Methods: A total of 1,238 patients with treatment naïve, firstly diagnosed CHC were enrolled from 7 tertiary hospitals in Korea from Jan 2008 to Dec 2011. Among them, 47(3.8%) HBsAg-positive CHC patients were detected. Clinical and virologic characteristics, interferon-based treatment rate and treatment efficacy, and the incidence of hepatocellular carcinoma (HCC) were evaluated.

Results: HBV/HCV co-infectees showed a lower mean age (57.4±10.2 years vs. 62.6±13.9 years, P<0.05) and higher proportion of male (64% vs. 50%, P=0.038) than HCV mono-infectees. Half of the co-infected patients (46.8%) had baseline HBV DNA level less than 2,000 IUL/mL and 23% of were positive for HBeAg. HCV genotype 1 and 2 was observed in 50% and 45%, respectively. Antiviral treatment was initiated in 56% of the co-infected patients, which was not different from that of HCV mono-infected group. Though 73% of patients who underwent antiviral treatment experienced adverse events, one fourth (26.3%) withdrew the treatment. The overall sustained virologic response rates were 65% and 86% in genotypes 1 and 2, respectively, which were similar to those of HCV mono-infected group. The incidence of HCC was 7.7% in co-infected group compared with 8.3% in mono-infected during a median 26 months of follow-up.

Conclusions: The prevalence of HBV/HCV co-infection in Korea was 3.8% showing younger and male-dominant feature. The clinical characteristics and the treatment efficacy were similar to that of HCV mono-infection. The comparative HCC incidence during follow-up will be presented.

Keywords: Co-infection, Hepatitis B, Hepatitis C

O - 042

How Many Chronic Hepatitis C Patients Would Be Treated More in DAA Era?

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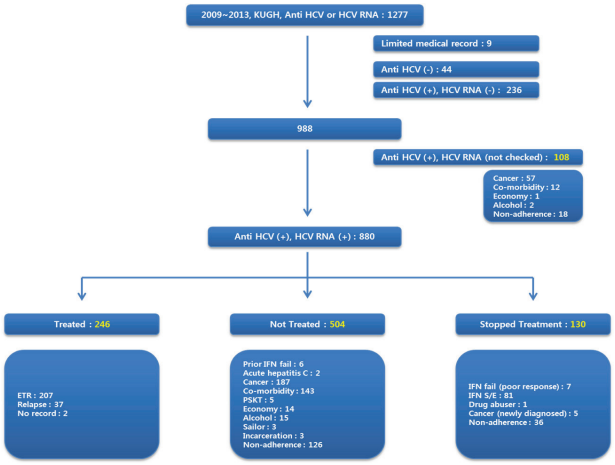
Aims: Interferon based treatment were not applicable to the large numbers of chronic hepatitis C patients, because of many kinds of medical and social reasons. However, newly developed DAA therapy has been applied to chronic hepatitis C patients without severe adverse effects and achieved nearly 80~90% SVR rate in a short treatment duration. So, we have been interested in how many chronic hepatitis C patients could be treated more with DAA in a real clinical situation of Korea.

Methods: From January 2009 to December 2013, medical records of patients who had been checked the serum Anti-HCV or serum HCV RNA in Kosin University Gospel Hospital were reviewed retrospectively,



focused on the reason for nontreatment of chronic hepatitis C.
Results: 1277 patients were checked Anti-HCV or HCV RNA. 108 patients did not checked the serum HCV RNA because of medical (64%), social (3%) conditions and non-adherence (33%). 880 patients were positive in both Anti-HCV and HCV RNA. 504 patients were not treated for the following reasons : 68% medical contraindications, 25% non-adherence, 4% social conditions, 3% ongoing alcohol abuse. 130 patients had to be stopped on the way of interferon based therapy : 68% attributed to interferon itself, 27% non-adherence, 5% medical and social conditions. Only 246 patients could be treated appropriately with interferon based therapy. But, more than 15% of treated patients were diagnosed of HCV relapse eventually.
Conclusions: Only small portion of chronic hepatitis C patients could be treated with interferon based therapy (28%). Newly developed DAA treatment would rescue the chronic hepatitis C patients who were not applicable to interferon based therapy because of medical (18%), social (1%) conditions and interferon itself (15%). Nevertheless, not all of the chronic hepatitis C patients would be treated with DAA in real clinical situation because of various unexpected reasons.
Keywords: Hepatitis C, DAA, Rescue, Interferon

O - 043

Daclatasvir plus Asunaprevir in Interferon (± Ribavirin)-Ineligible/Intolerant Asian Patients with Chronic HCV Genotype-1b Infection

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Aims: The efficacy/safety of daclatasvir (pan-genotypic NS5A inhibitor) plus asunaprevir (NS3 protease inhibitor) in interferon (± ribavirin)-ineligible/intolerant patients with chronic HCV genotype-1b infection from mainland China, Korea and Taiwan was investigated in a phase 3, open-label study.
Methods: Patients received daclatasvir 60 mg (tablet) once daily plus asunaprevir 100 mg (soft capsule) twice daily for 24 weeks. The primary endpoint was sustained virologic response at post-treatment Week 24 (SVR24).
Results: This study treated 159 patients from mainland China (80%), Korea (11%) and Taiwan (9%), including patients with cirrhosis (33%), IL28B non-CC genotypes (40%), and aged ≥70 years (4%). SVR24 was achieved by 91% of patients (100% concordance with SVR12) and was similarly high in all subgroups, e.g. cirrhotic patients (90%), and in patients from mainland China (91%), Korea (94%) and Taiwan (87%). SVR24 was higher in patients without baseline NS5A (L31M/Y93H) resistance-associated variants (RAVs) (n=137/139 [99%]), regardless of the presence (98%) or absence (99%) of cirrhosis, and lower in patients with baseline NS5A RAVs (n=8/19 [42%]). All serious adverse events (AEs) (n=5/159 [3.1%]), grade 4 laboratory abnormalities (n=3/159 [1.9%]) and deaths (n=1/159 [0.6%]) that occurred on-treatment were unrelated to the study drugs; two patients discontinued due to AEs. Treatment was generally well tolerated regardless of cirrhosis status.
Conclusions: Daclatasvir plus asunaprevir achieved a high SVR24 rate of 91%, rising to 99% in patients without baseline NS5A RAVs, and was generally well tolerated in cirrhotic and non-cirrhotic interferon (± ribavirin)-ineligible/intolerant patients with HCV genotype-1b infection from mainland China, Korea and Taiwan.
Keywords: Chronic HCV, Genotype-1b, Asian patients, Daclatasvir, Asunaprevir, IFN ineligible/intolerant

O - 044

ONYX-I: Efficacy of Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir in South Korean and Taiwanese Patients with HCV Genotype 1b Infection and without Cirrhosis

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Background: Approximately 45-50% of Hepatitis C virus (HCV) infections in South Korea and Taiwan are genotype (GT) 1b. Previous phase 3 studies demonstrated that the direct-acting antiviral (DAA) regimen of ombitasvir (OBV), ritonavir-boosted paritaprevir (PTV/r; identified by Abbvie and Enanta) and dasabuvir (DSV) was well tolerated and achieved sustained virologic response at post-treatment week 12 (SVR12) in 99% of treatment-naïve and 100% of treatment-experienced patients with HCV GT1b. ONYX-I (NCT02517515) was designed to evaluate efficacy and safety in Asian patients with HCV GT1b infection without cirrhosis.

Methods: Treatment-naïve and IFN-based therapy-experienced patients with HCV GT1b infection in South Korea, Taiwan, and China were randomized 1:1 to receive either OBV/PTV/r (25 mg/150 mg/100 mg once daily) and DSV (250 mg twice daily) or placebo for 12 weeks during the double-blind (DB) period. Patients in the placebo arm subsequently received OBV/PTV/r + DSV for 12 weeks during the open-label period. Patients will be followed for 48 weeks after last dose of study drugs. The primary objectives are to compare the SVR12 rates for the treatment-naïve and -experienced patients to corresponding historical SVR rates of telaprevir + peg-interferon and ribavirin therapy, and assess the safety of the OBV/PTV/r + DSV regimen. Presented are results from the South Korean and Taiwanese populations.

Results: In both South Korea and Taiwan, 120 patients were randomized and treated. Of South Korean patients, 45% were male, 33% were treatment-experienced and 89% had F0-F1 fibrosis. Of Taiwanese patients, 39% were male, 33% were treatment-experienced, and 87% had F0-F1 fibrosis. Safety data and SVR at post-treatment week 4 will be presented.

Conclusions: The ONYX-I study is evaluating the safety and efficacy of DAA regimen, OBV/PTV/r + DSV, in Southeast Asian patients without cirrhosis infected with HCV GT1b. Resultant data may help inform treatment guidelines for HCV GT1b in this population.

Keywords: Hepatitis C, Efficacy, Direct acting antiviral, SVR

O - 045

Analysis of the Efficacy and Safety of Daclatasvir and Asunaprevir in Korean Genotype 1b Chronic Hepatitis C Patients

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Aims: HCV genotype 1 has been known to be the most common and difficult to treat genotype worldwide under the treatment of pegylated interferon and ribavirin. The enhanced antiviral activity achieved by combining two direct-acting antiviral (DAA) agents, daclatasvir and asunaprevir, has been studied and represent the treatment of choice in this population. However, there is a lack of real-world data of the treatment efficacy and safety of the combined drug in Korean patients.

Methods: A total of 126 HCV genotype 1b patients treated with daclatasvir 60mg once daily and asunaprevir 100mg twice daily for 24 weeks were retrospectively reviewed from 4 centers of the Gwang-Ju/Jeon Nam province from August 2015 to April 2016. The treatment efficacy (HCV RNA < 25 IU/mL at post-treatment week 12 (SVR12)) of the combined treatment was the primary endpoint for the analysis. Various clinical parameters including patient demographics, Child-Pugh score, presence of baseline resistance associated variants (RAV), HCV RNA, and adverse effects to treatment were analyzed.

Results: This study included 90 treatment-naïve patients (71.4%), 30 nonresponders (23.8%), and 6 intolerable/ineligible (4.8%) patients to previous treatment of pegylated interferon and ribavirin. The presence for RAV at baseline was positive in 4 patients with Y93H (3.3%) among the tested 120 patients (95.2%). 42 patients (33.3%) with Child-Pugh A liver cirrhosis were included in the study. The proportion of patients with SVR12 was 97.2% (35/36). Prominent alanine/aspartate aminotransferase increase (> 200 U/L) was noted in 1 patient (0.8%). Fatigue (10.3%), headache (6.34%), nausea (4.7%), asthenia (3.2%) and diarrhea (0.8%) were noted but did not lead to discontinuation of therapy.

Conclusions: In HCV genotype 1b infected patients in Korea, Daclatasvir plus asunaprevir is well tolerated and provide high sustained virologic response. Studies to establish the predicting factors related to treatment response is further required.

Keywords: Chronic hepatitis C, Daclatasvir, Asunaprevir, Efficacy

O - 046

Incidence, Epidemiological Characteristics and Transmission of Sharp Injury in Health Care Workers in a Korean University Hospital during 2011-2015

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Aims: Health care workers (HCW) are at high risk of sharp injury including needle stick injuries, percutaneous and mucocutaneous injuries. Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) are causes of sharp injury-related infection. The aims of this study were to elucidate the incidence density and epidemiological characteristics of sharp injury among HCW, and to investigate the transmission rate of HBV, HCV and HIV in a Korean university hospital.

Methods: This retrospective cohort study analyzed the data from the HCW self-reporting system for sharp injury, which is integrated in electronic healthcare recording system and managed by Occupational Safety and Health Office from January 2011 to December 2015. The incidence density per 100 persons (full-time equivalent employees)-year of sharp injury was calculated. Descriptive analysis was performed on the characteristics of sharp injury and transmission rate of HBV, HCV, and HIV.

Results: A total of 1,076 occupational blood exposures were reported during 5 year. The total HCW number was 10,452, and the average yearly bed number was 1,072. Overall incidence density of sharp injury was 5.6 cases per 100 person-year, and 20.3 per 100 bed-year. Among the occupation type, housekeeping people in janitorial service company working in hospital wards showed the highest rate of sharp injury (14.8%) followed by doctors (8.5%) and nurses (6.2%). The most common place of sharp injury was wards, emergency room, and operating room (38.1%, 13.3% and 12.2%, respectively). The percutaneous injury accounted for 86.7% and mucocutaneous injury for 13.2%. During the 5 years, incidence rate tends to gradually decrease, and bed number per HCW was significantly associated with incidence density of sharp injury during the study period. Among the source patients, HBV, HCV, and HIV was positive in 133/681 (19%), 126/680 (18.5%) and 25/657 patients (3.8%), respectively. However, only one HCW was infected by HCV, showing HCV transmission rate of 0.8%. Neither HBV nor HIV infection occurred.

Conclusions: The current incidence rate of sharp injury in a Korean university hospital HCW by highly encouraged easy reporting system was 5.6 cases per 100 person-year, and 20.3 per 100 bed-year, showing the highest incidence in housekeeping people in janitorial service company working in hospital wards. The transmission rate of HCV was less than 1%, while there was no transmitted case of HBV or HIV. Preventive measures to reduce sharp injury for HCW should be continued.

Keywords: Healthcare workers, Needle stick injury, Occupational blood exposure, HCV, HBV, HIV

O - 047

Comparing the Clinical Features and Outcomes of Acute Hepatitis E Viral Infections with Those of Acute Hepatitis A, B, and C Infections in Korea

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Aims: Genotype 3/4 hepatitis E virus (HEV) is an emerging infection in developed countries. This study investigated the etiology of acute viral hepatitis, and compared the clinical features of HEV infections with those of hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections in Korea.

Methods: This study included 116 consecutive patients who were diagnosed with acute viral hepatitis between January 2007 and January 2016. Acute viral infections were observed in 23 patients with HEV (19.8%), 49 patients with HAV (42.2%), 28 patients with HBV (24.1%), and 16 patients with HCV (13.8%).

Results: The incidence of acute HEV infection was higher among older patients (median age: 49 years) and male patients (69.6%), and was associated with the consumption of undercooked or uncooked meat (43.5%). Most acute HEV infections were associated with pre-existing liver disease (e.g., alcoholic liver disease, chronic hepatitis B, biliary stones, and autoimmune hepatitis) and frequently presented with jaundice (56.5%). HEV-infected patients exhibited significantly lower median peak alanine aminotransferase levels (525 U/L), compared to HAV-infected patients (2,413 U/L, $P < 0.001$) and HBV-infected patients (1,356 U/L, $P = 0.001$). HEV-infected patients exhibited significantly higher median total bilirubin levels (6.8 mg/dL), compared to HCV-infected patients (1.2 mg/dL, $P = 0.028$). Two HEV-infected patients were diagnosed with Guillain-Barré syndrome, although no patients developed fulminant hepatitis.

Conclusions: Our findings indicate that HEV is no longer a rare cause of acute viral hepatitis in Korea.

Keywords: Hepatitis E virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus

O - 048

Daclatasvir plus Asunaprevir for Chronic Hepatitis C Virus Genotype 1b Infection: Real Life Data in Korea

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Aims: We conducted an interim analysis of real life data in Korean patients with genotype 1b HCV infection who were treated with daclatasvir plus asunaprevir.

Methods: One hundred eight patients with chronic HCV genotype 1b infection who were treated with daclatasvir plus asunaprevir in multicenters from July, 2015 were analyzed. HCV RNA at baseline, 4, 12, 24 weeks were assayed with laboratory tests. Resistant associated variant (RAV) were evaluated at baseline. Lower limit of HCV RNA quantification was 20 IU/ml. Significant adverse events were

defined as more than grade 3 according to CTCAE v4.0.
Results: Mean age was 60 years, 76 patients were treatment naïve (67%), and thirty patients had liver cirrhosis. RAV was observed in 3 patients (all Y93 positive). Median treatment duration was 16 weeks. 29 patients completed 24 week therapy (1 virologic breakthrough (VT)), while 9 patients stopped during therapy (3 VT, 2 adverse events, 4 economic burden), and 70 patients were on treatment. HCV RNA was not detected in 99/101 patients at 4 weeks (98.0%), 87/90 patients at 12 weeks (96.7%), and 31/34 patients at 24 weeks (91.2%). All four patients with VT had undetectable HCV RNA at 4 weeks. Two patients experienced VT at 12 weeks and other two at 16 and 24 weeks. All three patients with RAV completed 24 week therapy, and HCV RNA were not detected throughout 4,12, 24 weeks. Adverse event was observed in 39 patients (36%), including 2 significant adverse events (1 aminotransferase > 5 times UNL, 1 myalgia). SVR rate will be analyzed after further follow up.
Conclusions: In our patients, daclatasvir plus asunaprevir showed comparable efficacy and safety with previous clinical studies. More data in large population are needed including SVR results.
Keywords: Daclatasvir, Asunaprevir, HCV

6. Liver Cirrhosis, Clinical

June 17, 2016 | 16:30-18:10

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Comparison of Daily Norfloxacin versus Weekly Ciprofloxacin for the Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients: A Randomized Controlled Trial

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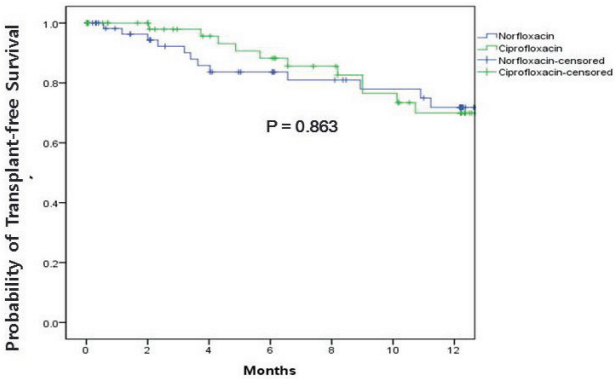
Aims: For the prevention of spontaneous bacterial peritonitis (SBP) in cirrhotic patients with ascites, norfloxacin 400mg per day is a standard regimen. However, ciprofloxacin 750 mg per week is also known to be effective. In addition, ciprofloxacin once weekly administration is more convenient and less costly. This study aims to prove that ciprofloxacin once weekly administration is as effective as norfloxacin once daily administration for the prevention of SBP.
Methods: Liver cirrhosis patients with ascites between 20-75 years old were screened, and enrolled in this randomized controlled trial if 1) ascitic polymorphonucleated cell count < 250/mm3 2) ascitic protein is equal or less than 1.5 g/dL or 3) the presence of history of SBP. Patients were randomly assigned into norfloxacin daily or ciprofloxacin weekly group, and followed-up for 12 months.
Primary end point was the prevention rate of SBP, and the secondary end points were 1 year mortality, incidence of infectious events, hepatorenal syndrome, and hepatic encephalopathy.



Results: 124 patients were enrolled and allocated into each group by 1:1 ratio (62:62). Male patients were 90% and the mean age was 55.2 ± 10.1. The mean Model for End stage Liver Disease (MELD) score was 14.6 ± 4.8. There was no difference in baseline characteristics between the groups. SBP developed in 2 patient of ciprofloxacin group, and in 3 patients of norfloxacin group (3.2% vs. 4.8%, P = 0.643). Cumulative transplant free survival rate were comparable between the groups (80.6% vs. 82.3%, P = 0.863). Incidence of infectious complication, hepatorenal syndrome, hepatic encephalopathy, and variceal bleeding rates were not significantly different (all P = ns). The only factor related to survival was underlying liver function (MELD, P = 0.001).
Conclusions: Once weekly ciprofloxacin was as effective as daily norfloxacin for the prevention of SBP in cirrhotic patients with ascites. [NCT01542801]
Keywords: Liver Cirrhosis, Ascites, Spontaneous Bacterial Peritonitis, Prophylaxis

O - 050

Transplantation with Autologous Bone Marrow-derived Mesenchymal Stem Cells for Alcoholic Cirrhosis: Phase 2 Trial

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Aims: Bone marrow-derived mesenchymal stem cell (BM-MSC) transplantation has been suggested as an effective therapy for liver cirrhosis. The efficacy and safety of autologous BM-MSC transplantation in the treatment of alcoholic cirrhosis (AC) were investigated.
Methods: Seventy-two patients with baseline biopsy-proven AC who had been alcohol-abstinent for more than 6 months underwent a multicenter, randomized, open-label, phase 2 trial. Patients were randomly assigned to three groups: one control group and two autologous BM-MSC groups that underwent either one-time or two-time hepatic arterial injections of 5×107 BM-MSCs 30 days after bone marrow aspiration. A follow-up biopsy was performed 6 months after enrollment and adverse events were monitored for 12 months. The primary endpoint was the improvement in the fibrosis-quantification based on Picrosirius-red staining. The secondary endpoints included liver function tests, Child-Pugh score, and the Model for End-stage Liver Disease score.
Results: In terms of fibrosis-quantification (before vs. after), one-time and two-time BM-MSC groups were associated with 25% (19.5±9.5% vs. 14.5±7.1%) and 37% (21.1±8.9% vs. 13.2±6.7%) reductions in the proportion of collagen, respectively (P<0.001). In the inter-group comparison, two-time BM-MSC transplantation in comparison with one-time BM-MSC transplantation was not associated with improved results in fibrosis-quantification (P>0.05). The Child-Pugh scores of both BM-MSC groups (one-time: 7.6±1.0 vs. 6.3±1.3 and two-time: 7.8±1.2 vs. 6.8±1.6) were also significantly improved following BM-MSC transplantation (P<0.05). The proportion of patients with adverse events did not differ among the three groups.
Conclusions: Autologous BM-MSC transplantation safely improved histologic fibrosis and liver function in patients with AC.
Keywords: Bone Marrow, Mesenchymal Stem Cell, Liver Cirrhosis, Transplantation

O - 051

Risk and Adverse Outcomes of Fractures in Patients with Liver Cirrhosis: Two Nationwide Studies

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Table 2. Risk of fracture events for cohorts with and without liver cirrhosis

		n	Person-years	Events	Incidence[a]	HR	(95% CI)[b]
All	No LC	15764	95430	1641	17.2	1.00	(reference)
	LC	3941	23221	675	29.1	1.83	(1.67-2.01)
Female	No LC	4980	29405	718	24.4	1.00	(reference)
	LC	1245	7352	249	33.9	1.53	(1.32-1.78)
Male	No LC	10784	66025	923	14.0	1.00	(reference)
	LC	2696	15869	426	26.8	2.04	(1.81-2.31)
Age, 20-39 years	No LC	2544	15955	183	11.5	1.00	(reference)
	LC	636	3838	97	25.3	2.12	(1.59-2.81)
Age, 40-49 years	No LC	3628	22574	295	13.1	1.00	(reference)
	LC	907	5601	142	25.4	2.04	(1.63-2.54)
Age, 50-59 years	No LC	3624	21828	332	15.2	1.00	(reference)
	LC	906	5442	124	22.8	1.67	(1.34-2.07)
Age, 60-69 years	No LC	3320	20111	373	18.5	1.00	(reference)
	LC	830	4903	144	29.4	1.69	(1.38-2.06)
Age, ≥70 years	No LC	2648	14963	458	30.6	1.00	(reference)
	LC	662	3437	168	48.9	1.70	(1.41-2.03)

CI, confidence intervals; OR, odds ratio;
[a]Per 1000 person-years.
[b]Adjusted for age, sex, low income, coexisting medical conditions, medication use. In the subgroup analysis, the ORs of traumatic brain injury, neck and trunk fracture, fracture of upper limb, fracture of lower limb, and hip fracture associated with liver cirrhosis were 2.28 (95% CI 1.66-3.14), 1.75 (95% CI 1.44-2.12), 1.78 (95% CI 1.52-2.08), 1.94 (95% CI 1.65-2.27), and 2.22 (95% CI 1.70-2.89), respectively.

Table 4. Adverse events after fracture in patients with liver cirrhosis

	No LC, %	LC, %	OR	(95% CI)*
30-day in-hospital mortality	1.3	2.2	1.60	(1.36-1.90)
Septicemia	2.6	5.5	1.71	(1.54-1.91)
Acute renal failure	0.7	1.3	1.59	(1.29-1.97)
Medical expenditure, USD[†]	2247±2616	2479±2758	p<0.0001	
Length of hospital stay, days[†]	8.7±14.5	9.6±10.5	p<0.0001	

CI, confidence interval; LC, liver cirrhosis; OR, odds ratio.
*Adjusted for age, sex, low income, medical center, coexisting medical conditions and types of fracture.
[†]Mean ± SD

Aims: Falls were identified as a complication for people with liver cirrhosis (LC). This study evaluated fracture risk and post-fracture outcomes in patients with LC.
Methods: We identified 3941 adults aged 20 years and older newly diagnosed with LC using the Taiwan National Health Insurance Research Database from 2000 to 2003. Comparison cohort consisted of 15764 adults without LC randomly selected by frequency matching in age and sex. Followed-up events of fracture from 2000 until 2008 were ascertained from medical claims. Adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) of fracture associated with LC were calculated in the multiple Cox proportional hazard models. Another nested cohort study of 600828 hospitalized fracture patients analyzed for adjusted odds ratios (ORs) and 95 % CIs of adverse events after fracture among patients with and without LC between 2006 and 2013.
Results: The incidences of fracture for people with and without LC were 28.0 and 16.9 per 1,000 person-years, respectively. Compared with control, the adjusted HR of fracture was 1.71 (95 % CI 1.55-1.87) for LC patients. Previous LC was associated with risks of septicemia (OR 1.87, 95 % CI 1.68-2.0), acute renal failure (OR 1.77, 95% CI 1.43-2.18), and mortality (OR 1.71, 95 % CI 1.45-2.01) after fracture.

Table 5. The stratification analysis in age, sex for the association between fracture patients

			30-day in-hospital adverse events*			
		n	Events	Incidence, %	OR	(95% CI)
Female†	No LC	285435	10039	3.5	1.00	(reference)
	LC	2303	198	8.6	1.98	(1.71-2.30)
Male†	No LC	308592	14657	4.8	1.00	(reference)
	LC	4498	363	8.1	1.58	(1.41-1.77)
20-29 years‡	No LC	68067	1751	2.6	1.00	(reference)
	LC	73	6	8.2	2.33	(0.99-5.51)
30-39 years‡	No LC	61255	1556	2.5	1.00	(reference)
	LC	664	43	6.5	1.75	(1.26-2.42)
40-49 years‡	No LC	73366	2038	2.8	1.00	(reference)
	LC	1302	114	8.8	2.35	(1.91-2.89)
50-59 years‡	No LC	94790	2758	2.9	1.00	(reference)
	LC	1261	87	6.9	1.79	(1.43-2.25)
60-69 years‡	No LC	82847	3046	3.7	1.00	(reference)
	LC	995	78	7.8	1.83	(1.44-2.32)
≥70 years‡	No LC	213702	13547	6.3	1.00	(reference)
	LC	2506	233	9.3	1.39	(1.21-1.60)
Fracture with surgery	No LC	400566	3334	2.7	1.00	(reference)
	LC	3334	239	7.2	2.10	(1.83-2.41)
TBI	No LC	109696	8157	7.4	1.00	(reference)
	LC	1172	148	12.6	1.60	(1.34-1.90)
Neck and trunk fracture	No LC	88832	4553	5.1	1.00	(reference)
	LC	1387	99	7.1	1.40	(1.13-1.72)
Upper limb fracture	No LC	218907	4219	1.9	1.00	(reference)
	LC	2051	94	4.6	1.73	(1.39-2.14)
Lower limb fracture	No LC	279792	13075	4.7	1.00	(reference)
	LC	3356	306	9.1	1.72	(1.52-1.94)

CI, confidence interval; LC, liver cirrhosis; OR, odds ratio.
†Multivariate adjustment except for sex.
‡Multivariate adjustment except for age.
*Any adverse events included with 30-day in-hospital mortality, septicemia, acute renal failure.

Conclusions: LC was associated with higher risk of fracture. Patients with LC had more complications and mortality after fracture. Fracture prevention and attention to post-fracture adverse events are needed for this susceptible population.

Keywords: Liver cirrhosis, Fracture, Risk, Adverse Outcomes

O - 052

Patients with Alcoholic Cirrhosis Had Higher Risk of Variceal Re-bleeding after Secondary Prophylaxis than Those with Virus-related Cirrhosis

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Background/Aims: Esophageal variceal bleeding is the leading cause of death in alcoholic cirrhosis patients. However, there has been no study directly comparing variceal bleeding of alcoholic liver cirrhosis patients with cirrhosis related to other etiologies. We aimed to compare the risk of variceal re-bleeding after secondary prophylaxis between alcoholic cirrhosis patients and virus-related cirrhosis patients.

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. Ratio of maximum to minimum platelet count/spleen diameter, reflecting fluctuation of portal pressure, in patients who experienced re-bleeding events was also evaluated.

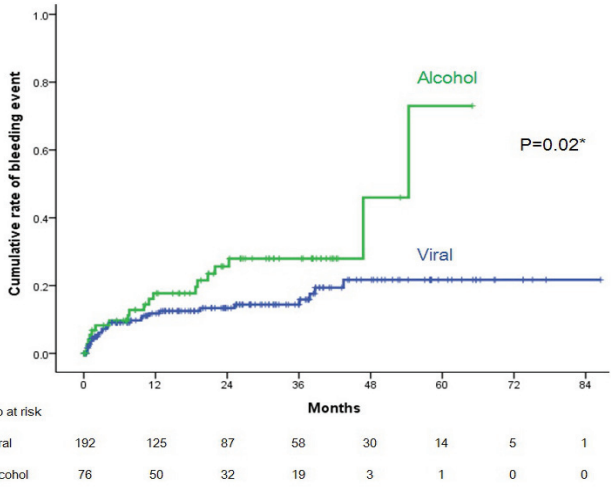

Figure 1. Kaplan-Meier estimates of re-bleeding risk after secondary prophylaxis

Results: A total of 268 patients were included: 76 in the alcoholic group and 192 in the viral group. During follow-up duration (median=21.5 months), 19 (25.0%) in the alcoholic group and 27 (14.1%) in the viral group developed re-bleeding. Median number of EVL sessions to achieving complete variceal obliteration was comparable between two groups (3.0 vs. 3.0; P=0.86). Multivariate analysis showed that the alcohol group (adjusted hazard ratio [aHR]=2.65, 95% confidence interval [CI]=1.40-5.04, P<0.01; Figure 1) was an independent risk factor after adjustment for hepatocellular carcinoma (HCC; aHR=2.84, 95% CI=1.42-5.71, P<0.01) and initial presentation as hematemesis (aHR=2.12; 95% CI=1.10-4.06; P=0.02). Analysis of re-bleeding patients with re-bleeding interval > 3 months showed that the alcoholic group had significantly higher ratio of platelet count/spleen diameter ratio than the viral group (mean=3.11 vs. 2.14; P=0.03).

Conclusions: Alcoholic cirrhosis patients has significantly higher risk of variceal re-bleeding compared to viral hepatitis patients, which might be related to fluctuation of portal hypertension related to re-current alcohol intake. The presence of HCC and initial presentation as hematemesis are other risk factors of re-bleeding.

Keywords: Esophageal variceal ligation, Esophageal varix, Bleeding, Recurrence

O - 053

The Impact of Kidney Dysfunction on Mortality in Cirrhotic Patients with Acute Deterioration

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Aims: This study aimed to investigate short-term mortality and associated factors in cirrhotic patients with kidney dysfunction and acute deterioration.

Methods: Of the 1204 cirrhotic patients experienced acute deterioration without kidney failure (defined as serum creatinine level of 2 mg/dL or above), 1094 patients (male 815, mean age 55.8 years) were retrospective consecutively collected during 2013. Kidney dysfunction was defined by serum creatinine levels from 1.2 to 1.9 mg/dL at admission based on retrospective KACLiF [Korean Acute-on-Chronic Liver Failure (ACLF)] study. Baseline characteristics and short-term mortality according to the presence of kidney dysfucntion were analyzed. Independent risk factors for 90-day mortality in patients with kidney dysfunction were obtained by multiple logistic regression.

Results: The prevalence of kidney dysfunction was 19.2% (210/1094). The 28-day and 90-day mortality were higher in patients with kidney dysfunction than in those without kidney dysfunction (12.4% vs. 4.4%, P < 0.001; 19.0% vs. 8.5%, P < 0.001, respectively). Eighty percent (32/40) of non-survivor was associated with the presence of ACLF and 18 out of 32 patients (56.2%) were ACLF development after admission. In multiple logistic regression, low albumin level (0.1 mg/dL increase, OR 0.90, 95% CI 0.81-0.99, P = 0.033) and the presence of ACLF (at admission, HR 11.4, 95% CI 3.8-33.6, P < 0.001; after admission, HR 30.8, 95% CI 9.9-95.8, P < 0.001) had independent factors of 90-day mortality. Especially, ACLF experience of grade 2 or above had higher mortality than grade 1 ACLF (P < 0.001).

Conclusions: In cirrhotic patients without kidney failure, kidney dysfunction with acute deterioration had a substantial mortality. To improve the mortality, it is necessary to endeavor to recognize the early renal dysfunction and to prevent additional organ failure and the progression of ACLF.

Keywords: Cirrhosis, Kidney, Liver failure, Mortality

O - 054

Cystatin C is Better than Creatinine for Predicting Prognosis in Cirrhotic Patients with Sarcopenia

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Aims: Recent studies suggested that serum cystatin C (CysC) is a better prognostic marker than serum creatinine (Cr) for predicting prognosis in patients with liver cirrhosis. Overestimation of renal function by serum Cr in these patients is associated with decreased muscle mass, which is represented by sarcopenia. This study was performed to evaluate the effect of sarcopenia on the prognostic efficacy of serum Cr and CysC levels in patients with liver cirrhosis.

Methods: Cirrhotic patients who performed abdominal CT and serum Cr and CysC levels were enrolled. Patients with hepatocellular carcinoma and parenchymal renal disease were excluded. At evaluation, transverse psoas muscle thickness (TMPT) was measured on a CT image at the level of the umbilicus. Sarcopenia was defined as TPMT/height <16.8 mm/m.

Results: A total of 245 patients were enrolled. Age was 55.0±10.2 years and 159 patients (64.9%) were men. Child-Pugh grade was A, B, and C in 121 (49.4%), 68 (27.8%), and 56 (22.9%) patients, respectively. Sarcopenia was noted in 110 patients (44.9%): 33.9%, 55.9%, and 55.4% in patients with Child-Pugh grade A, B, and C, respectively (P=0.003). Cr level were significantly lower in patients with sarcopenia compared to those without sarcopenia (0.7±0.2 vs 0.8±0.2 mg/dL, P<0.001), while CysC level did not (1.0±0.2 vs 1.0±0.3 mg/L, P=0.970). During 23.3±26.1 months of follow-up, 32 patients (13.1%) died. CysC level was significantly associated with survival of both patients with sarcopenia (P<0.001) and those without sarcopenia (P<0.001), while Cr level was not significantly associated with survival of patients with sarcopenia (P=0.760).

Conclusions: Serum Cr level was not useful for predicting prognosis in cirrhotic patients with sarcopenia, while CysC level was significantly associated with mortality regardless of the presence of sarcopenia. Serum CysC level is a better option for predicting prognosis in patients with cirrhosis, especially in those with sarcopenia.

Keywords: Sarcopenia, Liver cirrhosis, Creatinine, Cystatin C

O - 055

Differences in Cognitive Function between Patients with Viral and Alcoholic Compensated Liver Cirrhosis

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Aims: As alcohol induces change in frontal cortex primarily involved in cognition, cognitive function may be different between viral and alcoholic liver cirrhosis (LC). This study aimed to determine the differences of cognitive function between viral and alcoholic compensated LC.

Methods: From October 2011 to March 2013, 80 patients (viral: 37; alcohol: 43) with compensated LC were prospectively enrolled. Neuropsychological functions including attention, language, visuospatial, verbal memory, visual memory, and frontal/executive function were evaluated between two groups and compared with age-matched normal group (n=1,000). Cumulative incidence rate of overt hepatic encephalopathy (HE) was calculated. In the comparison with

normal group, both two groups showed decreased memory function, frontal/executive function, and Korea-Mini Mental Status Examination.

Results: In the analysis of two groups, memory function by Verbal Learning Test (recognition: 20.1±3.6 and 17.8±4.8, p=0.022), visuospatial function by Ray-Complex Figure Copy Test (recognition: 19.0±2.6 and 17.3±4.0, p=0.043), frontal/executive function by Controlled Oral Ward Association (semantic: 17.1±6.9 and 12.7±6.9, p=0.004), and the Korea-Mini Mental Status Examination (27.5±1.9 and 26.2±3.1, p=0.03) showed low scores in alcoholic compensated LC patients. The 1-, 2-, and 3-year cumulative incidence rates of overt HE were 23%, 26%, and 26% and 33%, 43%, and 49% in the viral and alcoholic compensated LC group, respectively (p=0.033).

Conclusions: Impaired memory and frontal lobe executive functions and early development of overt HE were more common in patients with alcoholic LC. For patients with alcoholic LC, more integrated tests for early detection of minimal HE and intensive treatment should be considered to prevent overt HE.

Keywords: Alcohol, Viral, Cognitive function, Cirrhosis

O - 056

Rifaximin Prolongs Overall Survival in Cirrhotic Patients Experiencing Hepatic Encephalopathy

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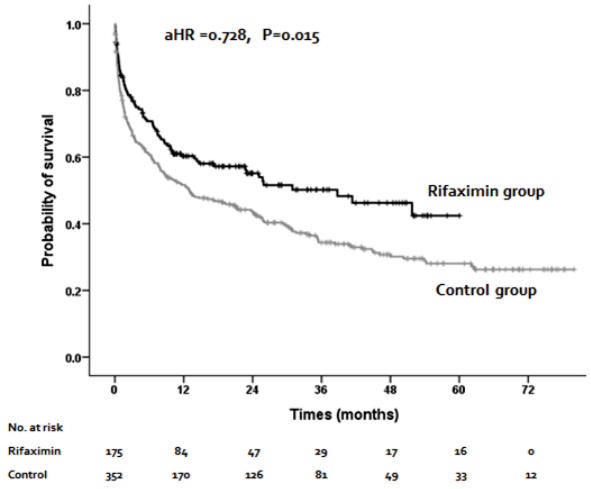
Aims: Recent studies suggested that rifaximin might decrease the risk of other portal hypertension-related complications by controlling small intestinal bacterial overgrowth. However, overall effect of rifaximin on cirrhotic patients has not been well evaluated in a large-scale cohort study. In this study, we aimed to evaluate whether rifaximin could prolong overall survival (OS) and reduce the risk of various cirrhotic complications other than hepatic encephalopathy (HE).

Methods: This retrospective study included 1,443 patients: 390 patients receiving rifaximin plus lactulose (the rifaximin group) and 1,053 patients receiving lactulose alone (the control group) for HE at a tertiary hospital in Korea. Primary endpoint was Overall survival (OS) and secondary endpoints included recurrence of HE, the development of spontaneous bacterial peritonitis (SBP), and variceal bleeding.

Results: The median follow-up period duration was 18.1 weeks (interquartile range, 7.0-76.0 weeks). During this time period, 788 (86.0%) patients died: 170 (43.5%) in the rifaximin group and 618 (58.7%) in the control group. In patients without hepatocellular carcinoma (HCC) (n=527), rifaximin significantly prolonged OS (adjusted hazard ratio (aHR) =0.728, 95% CI=0.563-0.941, P=0.015) after adjustment for age and Child-Pugh class (Figure 1). Rifaximin also significantly reduced the risk of recurrent HE (aHR=0.407, P<0.001),



SBP (aHR=0.367, P<0.001), and variceal bleeding (aHR=0.392, P<0.001); but not HRS (aHR=0.856, P=0.372). In patients with HCC (n=916), rifaximin treatment failed to prolong OS (aHR=0.937, P=0.454) and to reduce the risk of recurrent HE (aHR=0.767, P=0.175). However, rifaximin treatment significantly reduce the risk of SBP (aHR=0.461; P<0.001) and variceal bleeding (aHR=0.584, P=0.002) also in patients with HCC. The risk of C.difficile-associated diarrhea was not significantly different between groups (aHR=0.169; P=0.085).

Conclusions: In patients who experienced HE, rifaximin treatment significantly prolongs overall survival and reduces the risk of developing SBP, and variceal bleeding as well as recurrent HE, particularly in populations without HCC.

Keywords: Rifaximin, Liver cirrhosis, Hepatic encephalopathy, Overall survival

O - 057

Prediction of Clinical Outcomes in Patients with Biopsy-Proven Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy

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Aims: We sought to determine which factors lead to fatal events of end-stage liver disease, defined as variceal bleeding, refractory ascites, encephalopathy and hepatocellular carcinoma, and validate pre-existed treatment response criterions at 1 year to predict poor prognosis.

Methods: Since 2005 to 2015, 174 patients were diagnosed PBC with liver biopsy and their serum samples were collected for a median of 47.3 months, and approximately 10% (17 cases) presented fatal events of end-stage liver disease. The liver stiffness measurement (LSM) by transient elastography and serum markers of AST/ALT ratio, APRI, FIB-4, and Forns score were used to predict the poor prognosis.

And, the treatment response criterions at 1 year after UDCA treatment were validated with fatal events of end-stage liver disease.
Results: As a single predictive value, advanced fibrosis was the most powerful predictive factor with highest hazard ratio (HR) of 4.196 (1.458-12.075). With validation of pre-existed biochemical response criterions, Rotterdam criterion was superior to other criterions with the highest HR in univariate and multivariate analysis.
Conclusions: With noninvasive surrogate markers of transient elastography, AST/ALT ratio, APRI, and FIB-4 at diagnosis, we can classify high risk group of patients and after 1 year treatment with UDCA, by Rotterdam criterion, we can predict poor prognosis of patients accurately. This would provide us useful long-term prognostic information and make individualized management possible.
Keywords: Treatment response, Rotterm criterion, PBC, Prognosis prediction

O - 058

The Comparison of Long-term Survival in Cirrhotic Patients with Significant Ascites and Esophageal Varices According to the Treatment Modality between Endoscopic Variceal Ligation and Non-selective Beta-blockers

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Aims: Non-selective beta-blocker (NSBB) use has been established in the primary and secondary prevention of esophageal variceal hemorrhage. However, the use of beta-blockers in cirrhotic patients with ascites is still under debate. In this study, we compared overall survival (OS) in cirrhotic patients with ascites (≥grade 2) and esophageal varices according to their treatment strategies between endoscopic band ligation (EBL) and NSBB.
Methods: This retrospective study included consecutive 269 patients who were diagnosed as liver cirrhosis complicated with esophageal varices and ascites (≥grade 2) in a tertiary single center in Korea. Patients were divided into 3 groups which were EBL only, NSBB, non-treatment group. A Cox-proportional hazard analysis was performed to compare overall survival between the groups.
Results: The mean age was 53.8±10.9 years, and median follow-up duration was 37.7 months (IQR, 12.4-65.2). Overall survival was significantly shorter in the NSBB group followed by non-treatment group and EBL only group (median, 47.5 vs. 61.1 vs. 77.0 months; P=0.003). A multivariate analysis showed that the use of NSBB were an independent poor prognostic factor for shorter overall survival (adjusted hazard ratio, 1.98; 95% confidence interval, 1.31-2.98; P<0.001) after adjusted by Child-Pugh class.
Conclusions: The use of NSBB worsens the prognosis of cirrhotic patients with significant ascites. These results suggest that EBL is a more appropriate treatment option of esophageal varices when complicated with ascites (≥grade 2).
Keywords: Cirrhosis, Esophageal varices, Ascites, Survival

7. Liver Transplantation

June 17, 2016 | 16:30-18:10

O - 059

Factors Associated with Worse Outcome in Korean Split-liver Transplantation : Analysis of the 10-year Korean Network for Organ Sharing Data Base

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Purpose: Organ shortage has been a hot issue especially in the field of liver transplantation (LT) in Asian countries including Korea. In order to increase the donor pool, the policy of split LT (SLT) has been recently changed and recently number of SLT has been increased in Korea. However the outcome of SLT in Korea has not been reported.
Methods: This study evaluated the outcomes of SLT using the Korean Network for Organ Sharing (KONOS) between January 2005 and December 2014. Cases with two recipients from one deceased-donor were considered as SLT. A total of 200 cases of 100 pairs of SLT were examined.
Results: The recipient population was 107 adults and 93 children. The type of SLT composed of adult/children pair in 87 (87.0%). The median donor age and body weight were 25.0 (9~48) years and 66.3 (38~120) kg. Adult recipients' median age was 53.1 (25~77) years, and body weight 62.2 (35~101) kg. UNOS status 1 and 2A was 57 (53.3%) in adult recipients. The median donor / recipient weigh ratio (DRWR) was 1.12 (0.56~1.95); the DRWR<1.0 was 37.4%. Pediatric recipients' median age was 2.82 (0~16) year and body weight was 13.2 (range, 3.6~55) kg. The median DRWR was 6.80 (1.09~17.04); the DRWR>10.0 was 22.6%. UNOS status 1 in pediatric recipients was 10 (10.8%). The overall patients' survival outcome was 75.5%, but it was worse in adult recipients (67.3% vs. 84.9%) (Fig.1) (p=0.004). In adult recipients, prolonged prothrombin time (INR>1.5) of the donor and center sharing were poor prognostic factors in multivariate analysis (p<0.05).
Conclusion: Although the outcome of SLT in Korea was acceptable, the outcome was worse in urgent and big adult recipients, especially in cases of marginal donor with prolonged INR and low volume center. Further evaluation should be performed to make a good guideline for allocation of the deceased donor for SLT.

O - 060

Renal Function Difference between Anti-hepatitis B Immunoglobulin(HBIG) Monotherapy and HBIG Combined with Entecavir

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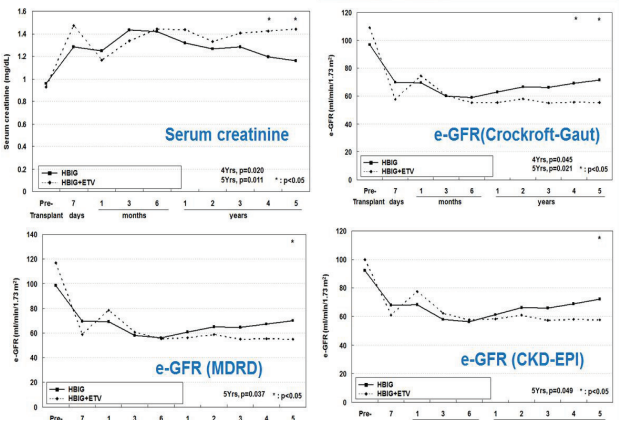
Aims: To reduce the HBV reinfection after liver transplantation, anti-hepatitis B immunoglobulin (HBIG) alone or combination with antiviral nucleotide analogues are usually used regimen. However, antiviral nucleotide analogues have nephrotoxicity, which is a critical issue because renal dysfunction frequently happens after liver transplantation.

Methods: Medical records of 171 liver recipients with HBV who underwent liver transplantation between Sep. 2005 and Dec. 2012 were retrospectively reviewed. The difference of renal function of HBIG mono-therapy group (HBIG) and HBIG combined with Entecavir group (HBIG+ETV) were analyzed.

Results: There was no significant difference in age, gender, body mass index, intraoperative blood loss, and MELD score between the two groups. But the patients who had preoperative ascites, mean preoperative AST level, preoperative GFR level, and the applying event of CRRT was significantly different between the groups. The decrease of eGFR between preoperative and 1 year after transplantation was 31.5±27.2 mL/min/1.73m2 (p<0.001), in HBIG group and 40.0±45.9 mL/min/1.73m2 (p<0.001) in HBIG+ETV group. Also, the eGFR decrease between preoperative and 4-year after transplantation was 24.5±29.9 mL/min/1.73m2 (p<0.001) in HBIG group and 38.9±56.8 mL/min/1.73m2 (p<0.001) in HBIG+ETV group.

Conclusions: There was no difference of recurrence rate of HBV. However, HBIG+ETV combination regimen showed more declination of eGFR in long-term period after liver transplantation than HBIG alone.

Keywords: Nephrotoxicity, Hepatitis B virus, Anti-hepatitis B immunoglobulin, Nucleoside analogue



O - 061

Hepatitis B Virus Immunoglobulin Is Internalized in Hepatocytes via Endocytosis and Induce Auto-phagosome

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Purpose: Hepatitis B immunoglobulin (HBIG) is used long time for prevention of hepatitis B virus (HBV) recurrence after liver transplantation. The HBIG is thought to bind and neutralize with virions or particles which have hepatitis B virus surface antigen (HBsAg) in serum. But according to more recent studies, investigated in vitro HBsAg specific immunoglobulin G (IgG) is internalized in hepatocytes. And HBIG can clearance to HBV with endocytosis in Fc receptors for IgG (FcRn) expression cell lines. The aim of this study was to investigate further mechanism of intracellular action of intravenouse human hepatitis B virus immunoglobulin (I.V. Hepabig) and Hepabig-gene in sense of more specific interaction with HBsAg. With respect to its mechanism of action, Hepabig or Hepabig-gene can effectively promote passive immunization for individuals exposed to the HBV by binding to HBsAg and reducing rate of replication.

Methods: The cell lines used in this study were: Huh7, HepG2, HepG2.2.15 (HBV-positive, HBsAg-positive) and PLC/PRF/5 (HBsAg positive). Human primary hepatocytes were isolated from resected partial liver. A variety of cell lines and isolated hepatocytes were exposed to 1) I.V.Hepabig, 2) recombinant Hepabig-gene and 3) Fab portion of Hepabig-gene for 1 hour. Confocal fluorescence microscopy was used to localize HBsAg specific IgG. Western blot analysis for the level of endogenous LC3 and HBsAg proteins was performed to identify autophage.

Results: HBsAg was colocalized with I.V. Hepabig, Hepabig-gene or Fab type in the cytoplasm as a punctate pattern of immunofluorescence in HBsAg expression cell lines (HepG2.2.15 and PLC/PRF/5). I.V. Hepabig also localized in cytoplasm with HBsAg in isolated primary hepatocyte from HBsAg positive human liver tissue. Western blot analysis proved that I.V. Hepabig and Hepabig-gene treated hepatocytes accumulated more intracellular HBsAg than control, but not in Fab type of Hepabig-gene treated hepatocytes. Especially, LC3-II which is lipidation of LC3-I form was detected with just Hepabig-gene treatment samples.

Conclusion: These results suggest that I.V. Hepabig and Hepabig-gene are present in FcRn expression hepatoma cell lines and primary hepatocytes by endocytosis and colocalized with HBsAg in the cytoplasm. Furthermore, the immunoglobulin-sAg complex induced autophgosom in the cytoplasm.

O - 062

Re-endotheliaization of Decellularized Porcine Liver Prevent Thrombosis

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Aims: The shortage of liver graft is obstacle for expansion of liver transplantation. Thrombosis developed in decellularized graft after blood perfusion when decellularized graft was used, these resulted in graft failure. Aims of present study were to show that the re-endothelization of decellularized porcine liver graft using endothelial cells prevent thrombosis.
Methods: Pre-conditioning for vascularization was used chemical agents (1-ethyl-3-(3-dimethylaminopropyl)carboniimide and N-hydroxysuccinimide) for heparinization and mouse anti-CD31 for antibody conjugation in decellularized procine liver graft. Thrombosis as end-point was evaluated after blood perfusion in vitro study.
Results: Decellularized porcine liver graft without re-endothelization developed thrombosis after blood perfusion. H & E and immunologic staining showed re-endothelialization in portal vein and hepatic vein. In vitro study, re-endothelialized porcine liver did not show thrombosis in the major blood vessels such as portal vein, superior and inferior hepatic inferior vena cava.
Conclusions: Re-endothelization using endothelials cells prevents thrombosis after blood perfusion in the decellularized porcine liver graft.
Keywords: Decellularization, Porcine liver, Bioengineering, Endothelialization

O - 063

Oncologic Outcomes of ABO-incompatible Living Donor Liver Transplantation for HCC Patients

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Aims: Liver transplantation (LT) is increasing treatment option for hepatocellular carcinoma (HCC). Over-immunosuppression is a risk factor for HCC recurrence after transplantation. But, there are a few report about the oncologic outcomes of ABO incampatibel (ABOi) LT. We analyzed post-transplant recurrence free survival of ABOi living donor liver transplantation (LDLT) for HCC recipients.
Methods: A total 237 recipients with HCC who underwent LDLT between January 2010 and December 2015 in Severance hospital were retrospectively reviewed. Among 237 patients, 23 patients underwent ABOi LDLT. We compared the characteristics and recurrence free survival of the patients after ABOi and ABOc LDLT.
Results: Clinical charateristics are not significantly different between ABOc and ABOi LDLT. The proportion of the patients beyond Milan criteria were not different in both group (13.1% and 13.0%). Among 237 patients, 33 patients (13.9%) experienced HCC recurrence after LDLT. The ABOc and ABOi LDLT group showed 14.0% and 13.0 of recurrence, respectively. Four-year recurrence free survival rates after LT were 81.6% in ABOc and 83.9% in ABOi group. Recurrence free survival rates of the ABOc and ABOi LDLT groups were not different when we analyzed the groups according to the Milan criteria (Figure 2).

Table 1. Patient characteristics

	ABOc (n=214)	ABOi (n=23)	p-value
Recipient age	54.38±7.50	54.35±5.12	0.981
Recipient sex (male)	177(82.7%)	20(87%)	0.605
Pre-transplant AFP	92.58±316.24	69.12±159.95	0.623
Within Milan criteria	186(86.9%)	20(87%)	0.996
Overall recurrence	30(14%)	3(13%)	0.898

Figure 1. Recurrence free survival curve after liver transplantation

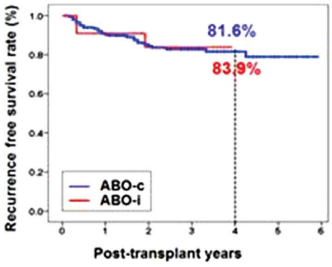
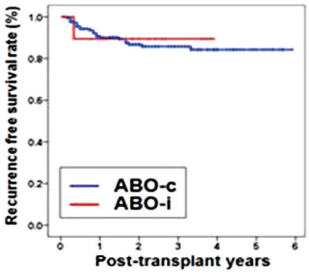
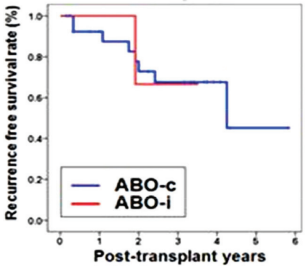


Figure 2. Recurrence free survival curve according to Milan criteri

a. Within Milan criteria



b. Above Milan criteria



Conclusions: The oncologic outcomes of the ABOi LDLT were not inferior to that of ABOc LDLT. Thus, ABO-incompatible liver transplantation can be safely performed for HCC patients.
Keywords: ABO-incompatible liver transplantation, Hepatocellular carcinoma, Living donor liver transplantation, Milan criteria

O - 064

Clinical Usefulness of mRECIST Response to Chemoembolization for Recurrence Estimation of Hepatocellular Carcinoma in Living Donor Liver Transplantation

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Aims: Predicting risk for recurrence of hepatocellular carcinoma (HCC) following living donor liver transplantation (LDLT) is clinically important. Response to preoperative transarterial chemoembolization (TACE) before LDLT has been recommended as a biological seclection criterion for LT to predict long-term outoutcom after LT. The aim of our study was to identify factors associated with recurrence of HCC after LDLT and to assess outcomes of LT recipients according to treatment response of TACE.

Methods: We performed a retrospective study for assessment of recurrence in 134 recipient who were diagnosed with HCC and performed LDLT following sequential transarterial chemoembolization (TACE) from January 2002 to March 2015 at a single institute. Treatment response was assessed using modified response evaluation criteria in solid tumors (mRECIST) categories: complete response (CR), partial response (PR),stable disease (SD) and progressive disease (PD).We assigned patients to the responder (RP, n=73) or non-responder (NR=61) group according to treatment response of TACE.the presence of mortality within 30 days after LT. Cox proportional hazard models and Kaplan-Meier analysis were utilized to estimate HCC recurrence.

Results: TACE responses were: CR=34.3%, PR=20.1%, SD=17.1% and PD=28.4%. Five-year HCC recurrence rate was 9.3% in patients responding to TACE (CR or PR), versus 40.8%, among patientswho did not respond (SD or PD, P=0.000). In multivariate analysis, independent pre-LT predictors of recurrence were pre-LT above Milan(P=0.002), size of larger explant tumor (P=0.015, >3cm vs. ≤3 cm), and presence of vascular invasion (P=0.0007).

Conclusions: TACE response in terms of mRECIST criteria may predict HCC recurrence. However, This has not been proven at the multivariate analysis unlike beyond Milan criteria and the presence of vascular invasion in the LDLT recipient. Further larger study is needed to justify clinical usefulness of mRECIST response to chemoembolization for recurrence estimation of hepatocellular carcinoma in living donor liver transplantation.

Keywords: Hepatocelluar carcinoma, Liver transplantation, Recurrecence, TACE

O - 065

Results of Living Donor Age of Sixth Decade for Adult Liver Transplantation Using a Right Lobe Graft

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Purpose: The number of available living donors per recipient is very limited, thus the use of old-aged living donor has been sometimes inevitable. Prognostic impact of donor age on the outcome of adult living donor liver transplantation (LDLT) was assessed.

Methods: Study population was adult recipients of right-lobe graft LDLT from January 2009 to December 2015. There were 18 living donors with age of 50 years or older (old-donor group). For control group for comparison, donors in their twenties (young-donor group) were selected after matching with sex, model for end-stage liver disease (MELD) score and primary diagnosis. Aged donors were more strictly selected than the young donors, especially for the proportion of future liver remnant ≥35% of total liver volume and minimal fatty change (<10%).

Results: Donor ages were 52.5±1.5 years versus 25.4±3.1 years in old- and young-donor groups, respectively. The remnant volume of donors was 38.9±3.0% versus 38.1±2.9%, respectively (p<0.05). One-month remnant liver regeneration rate was 103.1±10.6% versus 104.5±11.8%, respectively (p<0.05), and there was no difference in the incidences of donor complications. MELD score was 13.5±8.4 versus 15.7±7.5 in old- and young-donor groups (p<0.05). GRWR was 1.02±0.19 versus 1.168±0.18, respectively (p<0.05). In the recipients of both donor groups, biliary complication occurred in a similar rate (11% versus 10%, p<0.05) and there was no difference in the 5-year survival rate (94% versus 100%. p<0.05). However there was one in-hospital mortality case in the recipients of old-donor group because of a primary non-function graft.

Conclusion: Right lobe grafts from old donors of 50 years or older showed usual recovery of graft function and liver regeneration. Thus, the transplanted liver size, GRWR >1.0, and even complete surgical techniques of vein reconstruction (e.g. IRHV, MVH) must be considered with the status of the recipient prior to the transplantation. we suggest prudent donor selection (near 40% of remnant liver volume) to provide fully qualified partial liver graft and to ensure donor safety.

O - 066

Efficacy of Rabbit Anti-thymocyte Globulin for Steroid-resistant Acute Rejection after Liver Transplantation

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Aims: Acute cellular rejection after liver transplantation (LT) can be treated with steroid pulse therapy, but there is no ideal treatment for steroid-resistant acute rejection (SRAR). We aimed to determine the feasibility and potential complications of rabbit anti-thymocyte globulin (rATG) application to treat SRAR in liver transplant recipients.

Methods: We retrospectively reviewed medical records of 429 recipients who underwent LT at Severance Hospital between January 2010 and March 2015. We compared clinical features and graft survival between patients with steroid-sensitive acute rejection (SSAR; n=23)

and SRAR (n=11). We also analyzed complications and changes in laboratory findings after 2.5 mg/kg rATG treatment in patients with SRAR for 6-10 days.

Results: There were no significant differences in gender, age, Model for End-stage Liver Disease score, Child-Turcotte-Pugh score, or original liver diseases between patients with SSAR and SRAR, although deceased donors were more frequently associated with the SRAR group (P=0.004). All SRAR patients responded positively to rATG treatment; after treatment, the patients' median AST levels decreased from 138 to 63 IU/L, and their median ALT levels dropped from 327 to 70 IU/L 1 day after rATG treatment (P=0.022 and 0.017, respectively). Median AST, ALT, and total bilirubin levels significantly decreased 1 month post-treatment (P=0.038, 0.004, and 0.041, respectively). Median survival after LT was 23 months, and median survival after rATG was 22 months in patients with SRAR. Adverse effects included hepatitis C virus (HCV) reactivation, fungemia, and cytomegalovirus (CMV) infection. Nine SRAR patients survived with healthy liver function, one died from a traffic accident during follow-up, and one died from graft-versus-host disease and fungemia.

Conclusions: Administration of rATG is an effective therapeutic option for SRAR with acceptable complications in liver transplant recipients. However, occurrence of HCV reactivation and CMV infection in LT patients should be monitored after rATG treatment in these patients.

Keywords: Rescue treatment, Anti-thymocyte globulin, Steroid-resistant acute rejection, Liver transplant

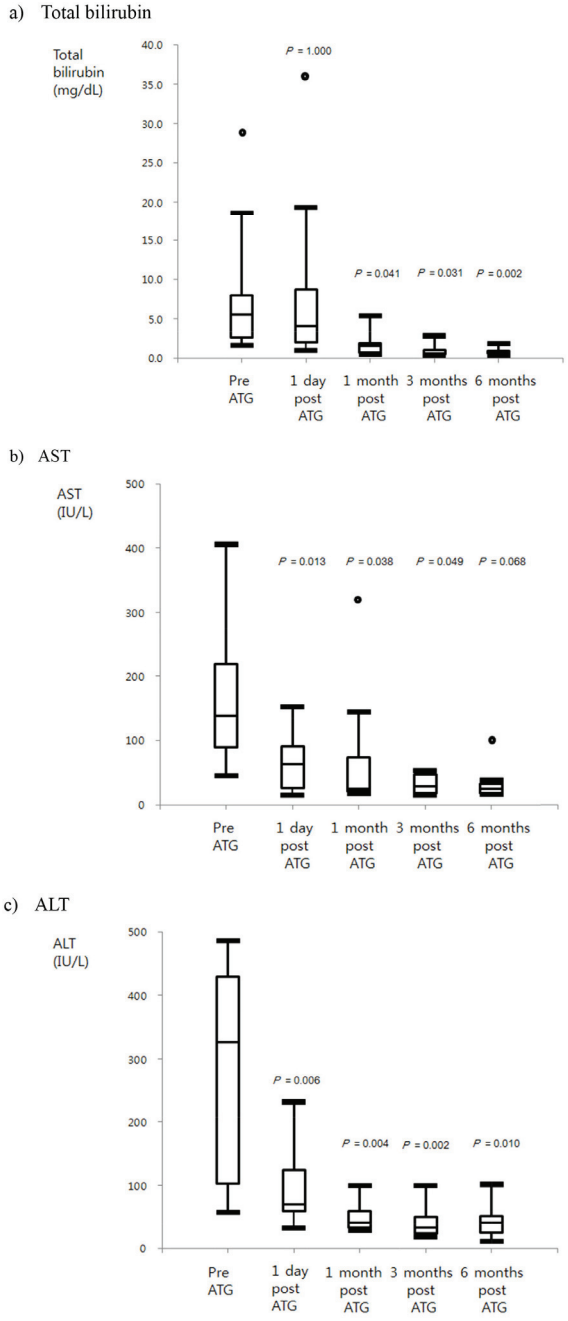

Figure 3. Surrogate laboratory markers pre- and post-ATG treatment for SRAR.

†p values were calculated by the Wilcoxon signed-rank test to compare laboratory changes from pre- ATG.

Abbreviations: ATG, antithymocyte globulin; SRAR, steroid-resistant acute rejection; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

8. HCC, Basic

June 18, 2016 | 13:50-15:30

O - 067

Modified AS1411 Aptamer Suppresses Hepatocellular Carcinoma by Up-regulating Galectin-14

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Aims: Aptamers are small synthetic oligonucleotides that bind to target proteins with high specificity and affinity. AS1411 is an aptamer that binds to the protein nucleolin, which is overexpressed in the cytoplasm and occurs on the surface of cancer cells. We investigated the therapeutic potential of aptamers in treating hepatocellular carcinoma (HCC) by evaluating anti-tumor effects and confirming the affinity and specificity of AS1411 and modified AS1411 aptamers in HCC cells.

Methods: Cell growth was assessed using the MTS assay, and cell death signaling was explored by immunoblot analysis. Fluore-

scence-activated cell sorting was performed to evaluate the affinity and specificity of AS1411 aptamers in SNU-761 HCC cells. We investigated the in vivo effects of the AS1411 aptamer using BALB/c nude mice in a subcutaneous xenograft model with SNU-761 cells.
Results: Treatment with a modified AS1411 aptamer significantly decreased in vitro (under normoxic [P=0.035] and hypoxic [P=0.018] conditions) and in vivo (under normoxic conditions, P=0.041) HCC cell proliferation compared to control aptamers. AS1411 and control aptamers failed to control HCC cell proliferation. However, AS1411 and the modified AS1411 aptamer did not induce caspase activation. Decrease in cell growth by AS1411 or modified AS1411 was not prevented by caspase or necrosis inhibitors. In a microarray, AS1411 significantly enhanced galectin-14 expression. Suppression of HCC cell proliferation by the modified AS1411 aptamer was attenuated by galectin-14 siRNA transfection.
Conclusions: The modified AS1411 aptamer suppressed HCC cell growth in vitro and in vivo by up-regulating galectin-14 expression. Modified AS1411 aptamers may have therapeutic potential as a novel targeted therapy for HCC.
Keywords: Aptamer, Hepatocellular carcinoma, Targeted therapy, AS1411, Nucleolin, Galectin-14

O - 068

Characterization of Cholangiocarcinoma-like Hepatocellular Carcinoma Using Gene Expression Pattern Analysis

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Aims: Hepatocelluar carcinoma (HCC), the most common primary liver cancer, shows very heterogeneous gene expression patterns compared with intrahepatic cholangiocarcinoma (CC). Recent studies revealed a subset of HCCs showing CC - like features in histopathologic and genomic levels. We tried to identify these overlapping tumors and to characterize this unique phenotype of HCC in clinical perspective.
Methods: Genomic data were downloaded from The Cancer Genome Atlas (TCGA) on human HCC (n=374) and intrahepatic CC (n=30). Using uniquely expressed genes between HCC and intrahepatic CC, total 52 tumors (13.9%) were predicted as "CC-like" phenotype among HCCs (BRB array tool, BCCP model, P<0.001, cut off probability = 0.1). We found uniquely expressed 1,122 genes (CC signature set) between CC-like HCCs and the other HCCs ((P<0.0001, four fold changes). Using the CC signature set, we identified CC-like subgroup in other independent HCC cohorts.
Results: Gene expression patterns of CC-like HCCs were significantly correlated with poor prognosis. They shared gene expressions with hepatic progenitor-origin tumors suggesting their origin might be shared with intrahepatic CC. The CC-like HCC also showed more aggressive gene expression patterns. Finally, CC-like HCCs showed significantly shorter overall survival than non-CC type in validation cohorts.
Conclusions: Unique phenotype of HCC exists sharing similar gene expressions with CC and its genetic features are correlated with aggressive tumor biology.
Keywords: Hepatocellular carcinoma, Cholangiocarcinoma, Gene expression, Prediction

O - 069

Opposite Roles of Cannabinoid Receptor 1 and 2 in Hepatocarcinogenesis

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Aims: The endocannabinoid system (ECS) exerts key roles in the development of liver fibrosis and fatty liver, two diseases that promote the development of hepatocellular carcinoma (HCC). Although cannabinoids exert potent anti-tumor effects in vitro, the contribution of the ECS to carcinogenesis in vivo remains elusive.
Methods: Expression of key components of the ECS, including endocannanabinoids, endocannabinoid-degrading enzymes and endocannabinoid receptors, was determined in healthy liver and tumors. Diethylnitrosamine-induced hepatocarcinogenesis was determined in mice deficient in fatty acid amide hydrolase (FAAH), the main anandamide (AEA)-degrading enzyme, in cannabinoid receptor (CB) 1-, CB2-, or transient receptor potential cation channel subfamily V member 1 (Trpv1)-deficient mice.
Results: Murine and human HCCs displayed activation of the ECS with strongly elevated expression of CB1 and CB2 but only moderately altered endocannabinoid levels. Contrary to the anti-tumor effects of cannabinoids in vitro, we observed increased hepatocarcinogenesis in FAAH-deficient mice, a mouse model with increased AEA levels. Accordingly, inactivation of CB1, the main receptor for AEA, in wild-type or FAAH-deficient mice suppressed hepatocarcinogenesis. In contrast, inactivation of CB2 increased hepatocarcinogenesis. CB1 was strongly expressed within HCC lesions and its inactivation suppressed proliferation and liver fibrosis. CB2 was predominantly expressed in macrophages. CB2 inactivation decreased the expression of T cell-recruiting chemokines, and inhibited hepatic T-cell recruitment including particular CD4+ T cells, a population with known anti-tumor effects in HCC. TRPV1 deletion did not alter HCC development.
Conclusions: Similar to their role in fibrogenesis, CB1 and CB2 exert opposite effects on hepatocarcinogenesis, and may provide novel therapeutic targets.

Keywords: Endocannabinoids, Hepatocellular carcinoma, Proliferation, Liver Fibrosis

O - 070

Clinical Relevance and Functional Role of Nuclear Met in Hepatocellular Carcinoma

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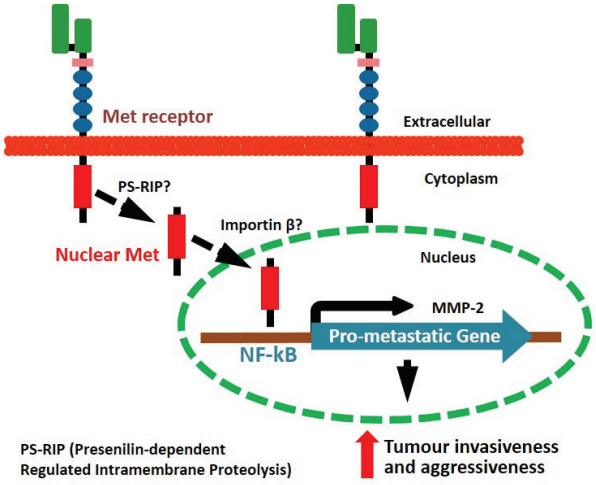
Aims: Met is a receptor tyrosine kinase which triggers a wide range of normal physiological signaling cascades. However, a perturbation of the Met pathway is commonly found in human cancers. Emerging evidence has shown the presence of nuclear Met in some cancerous tissues and cell lines, suggesting that nuclear Met could have unexplored functions in the nucleus. The present study aimed to assess the expression and functions of nuclear Met in hepatocellular carcinoma (HCC).

Methods: Nuclear Met expression of 103 clinicopathologically characterized HCC paired samples was examined by immunohistochemistry using an antibody against the carboxyl terminus of Met. Statistical analyses were applied to evaluate the association of nMet with different clinical parameters. Nuclear localization of Met was determined by western blot analysis and immunofluorescence microscopy. Met cytoplasmic fragments were characterized by *in vitro* functional assay such as migration, invasion and proliferation in HCC cells. Nude mice model was employed to investigate the *in vivo* functional impact of nuclear Met.

Results: Nuclear Met is overexpressed in nearly 90% of HCC paired samples and its expression is progressively increased along HCC development from non-tumorous liver tissue to advanced HCC. Nonetheless, nuclear Met overexpression is significantly associated with venous invasion and poorer overall survival. We found that nuclear Met, which has a lower molecular weight than Met, could only be detected using an antibody against the carboxyl terminus of Met (C28) in tumorous tissues. This finding strongly suggests that nuclear Met only comprises of the carboxyl cytoplasmic region of full length Met. Moreover, both western blot analysis of nuclear fraction of HCC cells and immunofluorescence confirmed the nuclear localization of Met. We designed construct J1, J3 and T2 that encode Met fragment truncated after tyrosine residues D972 and P1027 in the juxtamembrane region and after tyrosine kinase domain beginning at L1157, respectively. Immunofluorescence microscopy showed both J1 and J3 constructs are dominantly expressed in the nucleus whereas T2 construct is expressed in the cytoplasm. These observations indicated the region in between J1 and T2 as the important region that facilitates the nuclear localization of Met. *In vitro* functional assay showed that nMet significantly promoted HCC cell proliferation and anchorage independent growth. It also significantly augmented HCC cell migration and invasiveness. Besides that, nMet also enhanced HCC tumor formation in animal model. Furthermore, we showed that nMet promoted tumor invasiveness and aggressiveness through NF-κB/MMP2 pathway.

Conclusions: Nuclear Met is overexpressed and associated with venous invasion and poorer overall survival in HCC. We found that nuclear Met is actually the carboxyl terminal fragment of Met and translocates into nucleus to promote invasiveness in HCC cells.

Keywords: Nuclear met, Hepatocellular carcinoma, Nuclear translocation



O - 071

Dual Expression of CD133 and EpCAM Is Negatively Associated with Better Response to Sorafenib Treatment in Patients with Hepatocellular Carcinoma

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Aims: Sorafenib remains the only approved molecular targeted agent for hepatocellular carcinoma (HCC); however, reliable biomarkers are still lacking. The aim of this study was to explore the predictive role of stemness-related markers for sorafenib response in patients with HCC.

Methods: Forty-seven patients with HCC who had available tumor samples before starting sorafenib treatment were enrolled. RNA was extracted from formalin-fixed, paraffin-embedded samples, and real-time PCR was used to quantify mRNA expression of EpCAM, CD13, CK8, CD24, CD44, CD90, CD133, SALL4, ALDH1A1, albumin, and alpha-fetoprotein.

Results: Of 47 patients, 3 had combined HCC and cholangiocarcinoma. The predominant etiology for HCC was hepatitis B virus (72.3%). Most patients had preserved liver function (Child-Pugh class A, 89.4%), and 14.9% and 74.5% had vascular invasion or extrahepatic spread, respectively. No intrahepatic tumors were present in 34.0% of the patients. Patients with low CD133 expression tended to have longer progression-free survival (PFS) compared to those with high CD133 expression (5.5 months vs. 4.0 months, respectively; P=0.087), but this was not statistically significant. The expression of other markers was not associated with PFS. When combining two markers, patients with both low CD133 expression

and low EpCAM expression demonstrated better PFS compared to those who did not (7.0 months vs. 4.2 months, respectively; P=0.037).

Conclusions: Among patients with HCC given sorafenib, dual expression with CD 133 and EpCAM in tissue had a negative correlation with better prognosis. Expression of stemness-related markers CD133 and EpCAM may provide new insights about biomarkers for sorafenib therapy.

Keywords: Hepatocellular carcinoma, Sorafenib, Prognosis

O - 072

EKI1 (Epha2 Kinase Inhibitor 1) Suppresses Tumor Growth in Hepatocellular Carcinoma and Cholangiocarcinoma by Inducing Autophage and Apoptosis

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Aims: Erythropoietin-producing hepatocellular receptor tyrosine kinase subtype A2 (EphA2) is an attractive therapeutic target for suppressing tumor progression. EKI1 is coordination complex of zinc and known for its use in treating dandruff and seborrhoeic dermatitis. The aim of this study is to discover novel small molecules to inhibit EphA2 for the treatment of hepatocellular carcinoma and cholangiocarcinoma.

Methods: To discover novel and potent EphA2 inhibitors, we performed HTRF (Homogeneous time resolved fluorescence) kinase assay using the chemical library of Korea Chemical Bank and primary screened novel hit compounds. The enhancement of EKI1-mediated apoptosis and autophage were examined using immunoblotting and FACS analysis. Additionally, the antitumor effect of EKI1 was assessed using a mouse model.

Results: Thirty-six compounds screened as EphA2 kinase inhibitor by HTRF assay. We validated these substances related to inhibit cell proliferation and cell death. We identified EKI1, a effective theranostics based small molecules. Human hepatocellular carcinoma cell line and cholangiocarcinoma cell lines were treated various concentration of EKI1 for 12h. At low concentration of EKI1, proliferation of these cells was inhibited. At high concentration of EKI1, cell death was induced in these cells. As quantitatively assessed by flow cytometry, apoptosis was induced by EKI1 in cells. We investigated apoptotic signaling by Western blot and observed cleavage or overexpression of pro-caspase-7 and PARP in EKI1 treated cells compared with vehicle. The anti-proliferation effect of EKI was due to an increased autophage, which was confirmed by up-regulation of Autophagy protein 5 (Atg5), BECN and LC3 (autophagosome marker). In addition, EKI1 induced reactive oxygen species (ROS) in JCK and Huh7. We examined EKI1 up-or down-signal transduction pathways to use therapeutic target for HCC and CC. In vivo mouse model, tumor growth was suppressed in EKI1 injected mouse group compared with control group.

Conclusions: Our results revealed that autophage and apoptosis are involved in EKI1-mediated tumor cell death. Therefore, the EphA2 kinase inhibitor EKI1 is therapeutic target for hepatocellular carcinoma and cholangiocarcinoma.

Keywords: Theranostics, Epha2, Hepatocellular carcinoma, Cholangiocarcinoma

O - 073

Dichloroacetic Acid Promotes Hepatocellular Carcinoma Apoptosis via Reactive Oxygen Species Production

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Background/Aim: Dichloroacetic acid (DCA) is a pyruvate dehydrogenase kinase inhibitor which activates the citric acid cycle, increases reactive oxygen species (ROS), and induces apoptosis. Through modulating Warburg effect, DCA can reduce tumorigenesis and cancer progression in several cancer models. The aim of this study was to investigate the anti-cancer effect of DCA and to elucidate the mechanism in hepatocellular carcinoma (HCC) cells.

Methods: We performed *in vitro* experiments using human HCC cell lines (Huh-7 and SNU761). Hypoxic condition was induced using 1% O_2, 5% CO_2, 94% N_2. Tumor cell viability was assessed using MTS proliferation assay kit. After DCA treatment, the apoptosis pathway was examined using immunoblot analysis, and interaction with Death-inducing signaling complex (DISC) was examined using immunoprecipitation. ROS, pyruvate, citrate were also measured. To evaluate *in vivo* efficacy, we used subcutaneous mouse models.

Results: Treatment of DCA increased ROS production, and decreased pyruvate and citrate levels. DCA induced apoptosis in both intrinsic and extrinsic pathways, especially under hypoxic conditions. Caspase 8 and cellular FLICE-like inhibitory protein (c-FLIP) was activated to the DISC after DCA treatment. Inhibition of ROS using N-acetylcysteine attenuated the apoptosis signal induced by DCA. DCA showed tumor regression in the mouse model.

Conclusions: The results suggest that DCA induces cancer death through apoptosis, in particular, more efficiently in hypoxic environments. Therefore, DCA may have therapeutic potential in HCCs.

Keywords: Dichloroacetic acid, Hepatocellular carcinoma, Apoptosis

O - 074

Potentiated Anticancer Effects against Hepatocellular Carcinoma Cells by the Paradoxical Inhibition of Autophagy Resulting from Combining Everolimus with Ku0063794

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Aims: The critical role of the mammalian target of rapamycin (mTOR) pathway has raised the possibility of applying specific mTOR inhibitors

to halt cancer progression. While everolimus only inhibits mTORC1, Ku0063794 inhibits both mTORC1 and mTORC2.
Methods: Thus, we examined the ability of everolimus and Ku0063794, individually or in combination, to inhibit the growth of hepatocellular carcinoma (HCC) cells (HepG2 and Hep3B) both in an in vitro experiment and in vivo mouse xenograft model.
Results: HCC cells treated with both agents showed significantly lower rates of cell proliferation and higher apoptosis than HCC cells treated with the respective monotherapies (P<0.05). Unlike the monotherapies, combination therapy significantly decreased the percentage of HCC cells containing GFP-LC3 puncta, indicating reduced autophagosome formation (P<0.05). A reduction in autophagy induced by bafilomycin A1 promoted the pro-apoptotic effects of combination therapy, as demonstrated by higher expression of an apoptotic protein (Bim) and by lower expression of anti-apoptotic proteins (Mcl-1 and Bcl-xl). In addition, western blot analysis showed that combination therapy decreased the expression of SIRT1, which is known to promote autophagy. Overexpressing SIRT1 directly abrogated the pro-apoptotic effects of combination therapy, as evidenced by lower expression of an apoptotic protein (Bim) and higher expression of an anti-apoptotic protein (Mcl-1). In a nude mouse xenograft model, the shrinkage of tumors was more prominent in mice treated with combination therapy than in mice treated with the respective monotherapies, while equivalent total body weights were maintained in all groups (P<0.05).
Conclusions: Thus, our study suggests that combining everolimus and Ku0063794 potentiates the anticancer effects against HCC cells by inducing SIRT1 downregulation, resulting in decreased autophagy.
Keywords: MTOR, Everolimus, Hepatocellular carcinoma, Autophagy

O - 075

ERTC Involved in HCC Growth and Metastasis through p53 and WNK1 Signaling Pathway

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Aims: ERTC has been shown to be an important player in the regulation of centrosome/microtubule dynamics during mitosis and found to be deregulated in a variety of human malignancies. But, the functional role and signaling pathway of ERTC in hepatocellular carcinoma (HCC) remains elucidative.
Methods: ERTC mRNA and miR-1324 expression was confirmed by real-time PCR analysis in human liver sample. ERTC protein expression was investigated by immunoblotting analysis in HCC cell lines and HCC tissues. The ERTC expression was infected with adenovirus, or knockdown by a delivery with short hairpin RNA (shRNA) or treatment with the potential ERTC inhibitor KHS101 hydrochloride, in Huh7, HepG2, SH-J1 and Alexander cell lines; cells were analyzed for proliferation, migration, and invasion. Tumor metastasis by ERTC and WNK1 was tested in vivo mouse model. Moreover, signaling pathways involved in invasion and metastasis were analyzed by Western blot.
Results: ERTC was abundantly expressed in HCC cell lines and HCC tissues compared with non-tumor HCC tissues. ERTC mRNA was positively correlated with the tumor size, worsening differentiation status, lack of fibrous capsule formation, microvessel invasion, intrahepatic metastasis, AFP level and advanced stage of HCC. Knockdown of ERTC in SH-J1 and Alexander cells suppressed migratory and invasive behavior as well as the expression of EMT related markers. Silencing ERTC enhanced p53 expression and decrease phosphorylation of WNK1 in SH-J1 and Alexander cells. The cells with knockdown of ERTC using target shRNA reduced tumor metastasis in a lung metastasis mouse model. Moreover, knockdown of WNK1 also inhibit tumorigenicity and metastatic ability were examined in an orthotopic animal model. miR-1324 interacted with the 3′ untranslated region (3′ UTR) of ERTC. Levels of miR-1324 were correlated inversely with ERTC mRNA and in human HCC samples.
Conclusions: Therefore, ERTC may be involved in HCC growth and metastasis through p53 and WNK1 signaling pathway, which may be useful therapeutic targets.
Keywords: Hepatocellular carcinoma, ERTC, p53, WNK1

O - 076

Glypican-3 Aptamer Has Potential as a New Targeted Therapy for Hepatocellular Carcinoma

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Aims: Aptamers are single-stranded synthetic oligonucleotides binding to overexpressed molecular targets on cancer cells. Glypican-3 (GPC3), a cell surface oncofetal protein that is highly expressed in hepatocellular carcinoma (HCC), has emerged as a novel therapeutic target. We developed aptamers targeting GPC3 and assessed those therapeutic potentials in the treatment of HCC by evaluating the binding affinity to HCC cells and anti-tumor efficacy.
Methods: GPC3 expression on the surface of HCC cells (SNU-475, SNU-761, Huh7, and SNU-3058) was assessed by immunofluorescence staining. Flow cytometry was performed to determine the binding affinity of the GPC3 aptamers, which were generated through systematic evolution of ligands by exponential enrichment (SELEX) method, to HCC cells. Cell proliferation was studied using the MTS assay, and signaling pathways were explored by immunoblot analysis.
Results: GPC3 was highly expressed in all HCC cell lines tested. Fourteen SELEX-derived GPC3 aptamers (representative aptamer;

Kd, 4.5 ± 1.0 nM; Bmax, 0.45 fmol/mg protein) were evaluated using flow cytometry for selection of high-affinity aptamers to HCC cells. Among GPC3 aptamers analyzed, four GPC3 aptamers which showed high affinity to SNU-761 (~18.3%) or Huh7 cells (~37.0%) were selected for MTS assay. Treatment with GPC3 aptamers significantly suppressed HCC cell growth under normoxic (SNU-761 cells, P=0.038 and P=0.005; Huh7 cells, P=0.011 and P=0.013) and hypoxic (SNU-761 cells, P=0.019 and P=0.054; Huh7 cells, P=0.031 and P=0.011) conditions compared to control aptamers. Yes-associated protein (YAP), an oncogene which triggers cancer cell proliferation, was suggested to be down-stream signal of GPC3. GPC3 aptamers catalyzed inactivation of YAP by promoting its phosphorylation, leading to attenuation of HCC cell proliferation.

Conclusions: We demonstrated that newly synthesized GPC3 aptamers can bind to HCC cells with high affinity and suppress HCC cell growth via inactivation of YAP. Further investigation of GPC3 aptamers as a novel targeted therapy for HCC is warranted.

Keywords: Aptamer, Hepatocellular carcinoma, Targeted therapy, Glypican-3, Yes-associated protein

9. Liver Cirrhosis, HCC and Clinical

June 18, 2016 | 13:50-15:30

O - 077

How to Define Splenomegaly in the Diagnosis of Liver Cirrhosis? : Significance of Splenic Volume Measurement Using Ultrasonography

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Aims: To date, there is no acceptable criteria of spleen size for the clinical diagnosis of liver cirrhosis even though the recent Baveno consensus states splenomegaly is an adjunctive finding to define liver cirrhosis. We evaluated how relevant spleen volume (SV) measured by ultrasonography is to liver fibrosis stage and investigated the optimal cut-off of SV for liver cirrhosis.

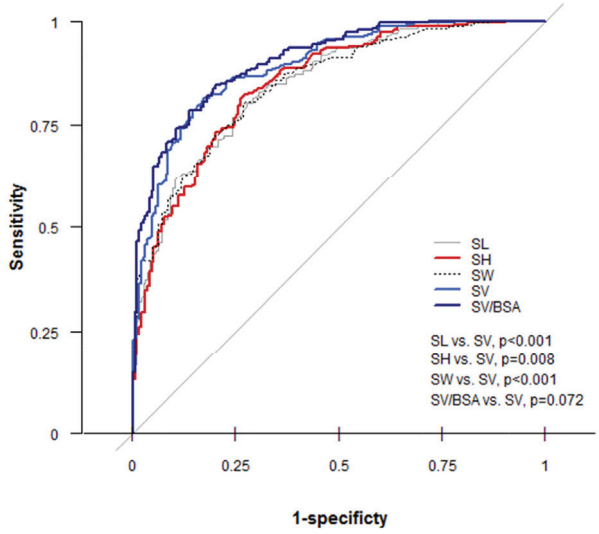
Methods: Total 431 patients whose SV was measured by ultrasonography (length x height x width x π/6) and got a liver biopsy for various reasons were included in this study. Spleen volume/body surface area (SV/BSA) in each patient was used for sensitivity analysis. Fibroscan score (kPa) was compared to SV for the relation with liver fibrosis stage. Clinical and laboratory findings were also collected.

Results: The baseline characteristics of the patients were as follows: mean age (49.1±12.2), slightly male predominance (223/431, 51.7%), mean BSA (1.7±0.2 m2), most common etiology of liver disease is hepatitis B (190, 44.1%), mean MELD score (9.7±4.1), Child-Pugh class [(A/B/C, 339(78.7%)/75(17.4%)/17(3.9%)], fibrosis stage [F0/F1/F2/F3/F4, 35(8.1%)/40(9.3%)/69(16.0%)/56(12.99%)/231(53.6%)]. SV was significantly larger in young age (<40), male sex, viral hepatitis, high BSA, high MELD and Child-Pugh score. SV was also well correlated with fibroscan score (r=0.509, p<0.001). Mean SV (ml) according to fibrosis stage was F0 (169±59), F1 (189±99), F2 (198±82), F3 (236±79), F4 (457±283). AUROCs of SV and SV/SBA for predicting cirrhosis were 0.891 (95% confidence interval, 0.862-0.921), 0.905 (95% CI, 0.878-0.932). Optimal cut-off of SV and SV/SBA for the diagnosis of cirrhosis were 268ml, 161ml respectively.

Table. Diagnostic performance for distinguishing fibrosis stage IV

Variable	F4 vs. Others							
	THR†	SEN	SPE	ACC	PPV	NPV	AUC (95% CI)	Comparison of AUC
Splenic length (SL)	≥10.425	177/231 (76.6%)	152/200 (76.0%)	329/431 (76.3%)	177/225 (78.7%)	152/206 (73.8%)	0.85 (0.814-0.885)	SL vs. SV, p<0.001 SHvs.SV,p=0.008 SWvs.SV,p<0.001 SV/BSAvs.SV,p=0.072
Splenic height (SH)	≥4.485	188/231 (81.4%)	148/200 (74.0%)	336/431 (78.0%)	188/240 (78.3%)	148/191 (77.5%)	0.851 (0.815-0.886)	
Splenic width (SW)	≥10.225	184/231 (79.7%)	147/200 (73.5%)	331/431 (76.8%)	184/237 (77.6%)	147/194 (75.8%)	0.849 (0.814-0.885)	
Splenic volume (SV)	≥268	188/231 (81.4%)	166/200 (83.0%)	354/431 (82.1%)	188/222 (84.7%)	166/209 (79.4%)	0.891 (0.862-0.921)	
Spelnic volume/BSA (SV/BSA)	≥161.3293	181/231 (78.4%)	173/200 (86.5%)	354/431 (82.1%)	181/208 (87.0%)	173/223 (77.6%)	0.905 (0.878-0.932)	

Abbreviation: THR, threshold; SEN, sensitivity; SPE, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.
† Threshold was computed by Youden's index.
Sensitivity,specificity,accuracy,PPVandNPVwerecalculatedfromthethresholdandthe95%CIofAUCwascomputedbyDelong'smethod.
AUCofthesplenicfactorwascomparedtotheAUCofsplenicvolumebyDelong'smethodandthep-valueswerecorrectedbyBonferroni'smethod.



Conclusions: SV measured by ultrasonography was closely associated with severity of liver disease and fibrosis stage. SV measurement using ultrasonography is useful as a supplementary method for the diagnosis of liver cirrhosis.

Keywords: Cirrhosis, Spleen volume, Ultrasonography

O - 078

Usefulness of Shear Wave Elastography (SWE) to Differentiate Diffuse Hepatic Diseases

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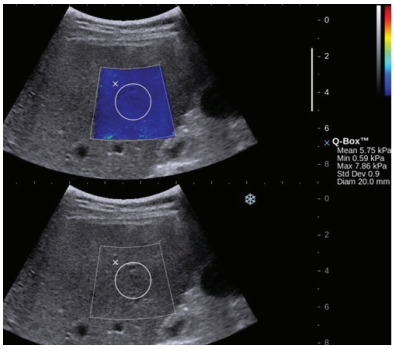
Aims: To evaluate the values of liver stiffness (LS) measured by Supersonic shear wave elastography (SWE) in diffuse hepatic parenchymal abnormalities in daily clinical practice and to find the difference according to severity and kinds of liver diseases.
Methods: Of 663 patients who underwent ultrasonography coupled with SWE, normal group (n=24) was defined as the person without any clinical evidence of underlying cause and normal laboratory and ultrasonographic features. Diffuse liver disease groups consisted of as follows: 1)fatty liver disease (n=136), 2)acute hepatitis (n=9), 3)chronic hepatitis (n=240), 4)cirrhosis (n=254) and cause of diseases are classified as 1)viral infection (n=327), 2)alcohol (n=175), 3)others (n=161) by clinicopathologic settings. We compared mean values and standard deviation (SD) provided by SWE and calculated median values.
Results: Mean values of LS was as follows: normal, 6.30±1.86kPa; fatty liver disease, 7.80±5.38kPa; acute hepatitis, 12.93±6.63kPa; chronic hepatitis, 8.54±5.58kPa; cirrhosis, 19.82 ±13.20kPa. The mean and median values in same patient were not significantly different in all comparison. There was significant difference of mean values and SD between cirrhosis and each other liver disease (p<.001). The measured values were not significantly different between normal group and fatty liver disease (p>0.1). According to causes of liver diseases, mean values of LS were significantly different: chronic hepatitis by virus, 8.14±4.20kPa; by alcohol, 12.56±11.22kPa (p<.005) and cirrhosis by virus, 15.22±11.74kPa; by alcohol, 25.58±13.61kPa (p<.001). LS in alcoholic chronic hepatitis or cirrhosis was 22.46±14.12kPa which was significantly higher than 8.46±8.44 in normal or fatty liver (p<.001) and that is same as in non-alcoholic patients, 11.26±9.49kPa and 7.29±3.78 (p<.001).
Conclusions: LS values by SWE are significantly higher in cirrhosis than in other hepatic diseases. In chronic hepatic diseases, LS in alcoholic patients are higher than in other causes.



Keywords: Elastography, Liver stiffness, Cirrhosis, Chronic hepatitis

O - 079

Accurate Prediction of Liver Fibrosis Using Noninvasive Markers in Korean Primary Biliary Cirrhosis Patients

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Aims: We aim to evaluate the performance of transient elastography and noninvasive serum markers of liver fibrosis in Korean primary biliary cirrhosis patients.
Methods: Since 2005 to 2015, 174 patients were diagnosed PBC with liver biopsy and their serum samples were collected for a median of 47.3 months. The liver stiffness measurement (LSM) by transient elastography and serum markers of AST/ALT ratio, APRI, FIB-4, and Forns score were used to evaluate the advanced fibrosis and the presence of cirrhosis.
Results: To compare to the minor fibrosis group, advanced fibrosis and presence of cirrhosis group had higher LSM, AST/ALT ratio, APRI, and FIB-4 score. As a single predictive factor for advanced fibrosis and cirrhosis, platelet count, LSM, AST/ALT ratio, APRI and FIB-4 score were statistically significant to predict, and with estimating the area under the receiver operating characteristic curve (AUROC) with each of them as a predictive factor, LSM showed most powerful predictability with AUC of 0.882. With the cut off value of 8.7 (kPa), it showed the sensitivity of 92.31% and the specificity of 76.00%, respectively.
Conclusions: Noninvasive serum markers, platelet, AST/ALT ratio, APRI, and FIB-4 score can be helpful to predict the significant fibrosis and LSM, with its high sensitivity, can be a good substitute for liver biopsy.
Keywords: PBC, Fibroscan, Noninvasive serum markers, Prediction of fibrosis

O - 080

Serum Wisteria Floribunda Agglutinin-positive Mac-2-binding Protein Level as a Predictor of Hepatic Fibrosis in Chronic HBV Infection

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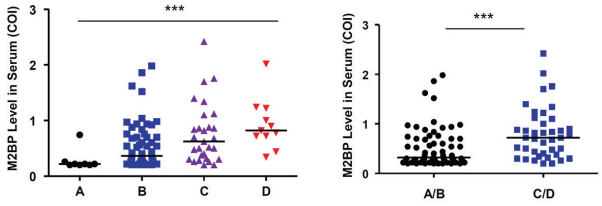
Aims: Wisteria floribunda agglutinin-positive Mac-2-binding protein (WFA+-M2BP) was recently identified as a biomarker for hepatic fibrosis in patients with chronic hepatitis C (CHC) infection, and it has also been proven as a predictive marker in patients with CHC-related hepatocellular carcinoma. In this study, we investigated the association between WFA+-M2BP levels and liver histological findings for patients with chronic hepatitis B virus (HBV) infection, comparing with transient elastography (FibroScan) measurements or the Enhanced Liver Fibrosis (ELF) score.
Methods: Biopsy proven, 106 chronic hepatitis B (CHB) patients with alanine aminotransferase (ALT) less than 150 were analyzed. We examined the effect of WFA+-M2BP level on severity of liver fibrosis,



comparing with transient elastography (FibroScan) measurements and the Enhanced Liver Fibrosis (ELF) score, a serum ECM marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA). Receiver operating characteristic curve (ROC) analysis was performed to calculate the area under the ROC (AUROC).

Results: The WFA+-M2BP value ranged from 0.2 cutoff index (COI) to 2.42 COI (median value, 0.55 COI). The median values in each Knodell fibrosis stage are: 0.22 COI in A, 0.38 COI in B, 0.62 COI in C, and 0.82 COI in D (P = 0.0044). For predicting liver cirrhosis (Knodell fibrosis stage D), WFA+-M2BP level had the AUROC of 0.753. By correlation analysis, serum M2BG level significantly correlated with ELF score (r2 = 0.1764, P < 0.0001) and FibroScan measurements (r2 = 0.2239, P < 0.0001). In the validation cohort, serum WFA+-M2BP levels were significantly higher in chronic hepatitis patients without cirrhosis and even higher in patients with liver cirrhosis than normal controls (P < 0.0001).

Conclusions: Our data suggest that the serum WFA+-M2BP value may be useful for predicting liver cirrhosis in patients with chronic hepatitis B infection.

Keywords: WFA+-M2BP, Hepatic fibrosis, Fibroscan, ELF score

O - 081

Diagnostic Value of AFP, AFP-L3, and PIVKA-II and Their Combinations for Hepatocellular Carcinoma: Single center, Case-control Study

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Background and Aim: Alpha-fetoprotein (AFP), Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), and protein induced by vitamin K absence or antagonist–II (PIVKA-II) are widely used as tumor markers for diagnosis of hepatocellular carcinoma. This study aimed to perform a head-to-head comparison of the diagnostic value of AFP, AFP-L3 and PIVKA-II as single or in combination to find the best biomarker or panel.

Methods: Seventy nine patients with newly diagnosed HCC and 77 non-HCC liver cirrhosis control patients were enrolled. Plasma AFP, AFP-L3, PIVKA-II levels were measured by ELISA, and receiver operating characteristic curve analyses were performed for each biomarker and for every combination of the markers.

Results: Among three single biomarkers, AFP showed the highest area under the curve (0.751, 95 % confidence interval0.683-0.818). The diagnostic performance (sensitivity/specificity) of each single biomarker was 68.35 %/81.82 % with AFP (AFP>40 ng/mL), 70.89 %/70.13 % with PIVKA-II (PIVKA-II > 40 mAU/mL), and 50.63 %/83.12 % with AFP-L3 (AFP-L3>10 %), respectively. In case of combination of the biomarkers, 'PIVKA-II > 40 mAU/mLand AFP>40 ng/mL' showed the highest AUC (0.765, 95 % CI:0.708-0.823), and its sensitivity and specificity were 55.70 % and 97.40 % each. Compared with combination of 'PIVKA-II > 40mAU/mL and AFP>40 ng/mL and AFP-L3>10 %' (sensitivity 40.51 %, specificity 98.70 %, AUC 0.696), it had better sensitivity (55.70 %*vs.* 40.51 %, p=0.001) and AUC (0.765 *vs.* 0.696, p=0.001) and similar specificity (97.40 %*vs.* 98.70 %, p=0.001). The combination of 'PIVKA-II > 40 mAU/mLor AFP>40 ng/mL or AFP-L3>10 %' showed the highest sensitivity (sensitivity 84.81 %, specificity 51.95 %, AUC 0.684), but compared to combination of 'PIVKA-II > 40 mAU/mLor AFP>40 ng/mL'(sensitivity 83.54 %, specificity 54.55 %, AUC 0.690), there is no statistical significant difference (p=0.549).

Conclusions: AFP showed the best diagnostic performance as a single biomarker for diagnosing HCC. Furthermore, when AFP combined with PIVKA-II, its diagnostic value could be maximized. However, AFP-L3 did not contribute to distinguish between HCC and non-HCC liver cirrhosis.

Keywords: Diagnostic value, Hepatocellular carcinoma, AFP, AFP-L3, and PIVKA-II

O - 082

Significance of Alpha-fetoprotein Variation in the Surveillance for Hepatitis B Virus-related Hepatocellular Carcinoma

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Aims: α-fetoprotein (AFP) is the most widely used biomarker in hepatocellular carcinoma (HCC) surveillance. Although AFP is periodically measured in real-world practice, most published literature on the performance of AFP-based HCC surveillance analyzed single representative values. Serial changes in AFP levels might indicate presence of HCC, but AFP levels might also fluctuate without HCC during the natural course of chronic hepatitis B virus (HBV) infection. The aim of this study was to determine whether information on the serial changes in AFP values may improve the test performance of AFP during surveillance for HBV-associated HCC.

Methods: A retrospective cohort of 4582 HBV-associated chronic hepatitis patients received HCC surveillance by means of AFP and ultrasonography. Development of HCC was evaluated for mean follow-up duration of 4.6 years. A total of 43028 AFP measurements were analyzed by ROC analysis. Serial changes in AFP levels were assessed by difference from baseline values (AFPdiff_base), differences from immediately previous result (AFPdiff_prev), Standard deviation value of AFP (AFPsd), numbers of episodes when AFP increased by 10 ng/mL compared to previous measurement.

Results: Baseline HBeAg positivity was 36.7% patients, and 32.3% of total showed liver cirrhosis clinically. During the median follow-up of 49 months, 80 cases of HCC were identified: the 10-y incidence was 4.1%. Baseline AFP was 17.7 ng/mL in HCC patients and 13.3 ng/mL in patients without HCC (P = 0.638). The ROC analysis showed that AFPsd showed best performance (AUC = 0.811), followed by numbers of AFP increase > 10 ng/mL (AUC = 0.734), both of which were significantly superior to AFP alone (AUC = 0.624), AFPdiff_prev (AUC = 0.600) or AFPdiff_base (AUC = 0.561).

Conclusions: Consideration of previous levels of AFP significantly increases the performance of AFP in the surveillance of HBV-associated HCC.

Keywords: Alpha-fetoprotein, Liver cirrhosis, Early detection of cancer, Hepatocellular carcinoma

O - 083

Multiplication of Tumor Volume by two Tumor Markers Is a Useful Predictor of Microvascular Invasion and Post-resection Prognosis in Solitary Hepatocellular Carcinoma

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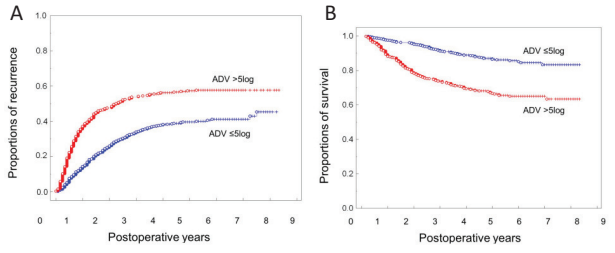
Purpose: We hypothesized that microvascular invasion (MVI) and the post-resection prognosis in patients with solitary hepatocellular carcinoma (HCC) could be predicted using blood tumor markers and tumor burden. Thus, we intended to identify a simple surrogate marker via a combination of clinical variables.

Methods: This retrospective study used a narrowly selected development cohort (n=1,176) and a validation cohort (n=551) containing patients who underwent curative resection of solitary HCC.

Results: In the development cohort, the median values were 13.7 mL for tumor volume (TV), 24.2 ng/mL for α-fetoprotein (AFP), and 75 mAU/mL for des-γ-carboxy prothrombin (DCP); there was no correlation among these three factors (r2≤0.237, p=0.000). The 1-, 2-, 3-, and 5-year rates were 22.4%, 34.4%, 41.7%, and 46.8% for tumor recurrence and 93.6%, 88.2%, 84.0%, and 78.2% for patient survival, respectively (Fig. 1). Independent risk factors for both tumor recurrence and patient survival were tumor diameter>5cm or TV>50 mL, MVI, satellite nodules, and high DCP. Multiplication of AFP, DCP, and TV (the ADV score) resulted in an MVI cutoff of 5log with a sensitivity of 73.9% and specificity of 66.7%. Patient stratification according to an ADV score with cutoffs of 5log alone or 6log/9log and combination with MVI showed significant prognostic differences (all p<0.000). This prognostic significance was reliably reproduced in the validation cohort (all p<0.000).

Conclusion: The ADV score is an integrated surrogate marker of HCC prognosis. We believe that it can be used to predict MVI and the post-resection prognosis before and after surgery.



Figurer 1. Tumor recurrence (A) and overall patient survival (B) curves according to an ADV score cutoff of 5log in the development cohort.

O - 084

Prognostic Impact of Complete Pathologic Response Following Preoperative Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma in Liver Cirrhosis Patients Undergone Liver Resection or Transplantation

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Purpose: This study aimed to assess the prognostic impact of complete pathological response (CPR: tumor necrosis ≥ 99%) after preoperative transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) on long-term survival outcomes in patients undergoing resection of liver resection (LR) or liver transplantation (LT).

Methods: The clinical outcomes of patients showing CPR after LR (n=110) or LT (n=233) were analyzed, with each control group of minimal risk (solitary HCC ≤ 2cm, absence of neoadjuvant treatment and R0 resection for LR control (n=476); one or two HCCs ≤ 2cm and absence of neoadjuvant treatment for LT control (n=184).

Results: In LR study group, 1-, 3- and 5 year tumor recurrence rates were 18.5%, 50.6% and 58.7% respectively, which are significantly higher than in RL control group (p=0.000); 1-, 3- and 5 year patient survival rates were 97.8%, 82.0% and 69.1% respectively, which are significantly lower than in RL control group (p=0.000). In LT study group, 1-, 3- and 5 year tumor recurrence rates were 4.1%, 7.9% and 7.9% respectively, which are significantly higher than in RT control group (p=0.019); 1-, 3- and 5 year patient survival rates were 92.7%, 89.2% and 86.9% respectively, which are not significantly lower than in RT control group (p=0.112). When comparing LR and LT study groups, tumor recurrence and patient survival curves showed significant differences (both p<0.000) (Fig. 1). The main site of tumor

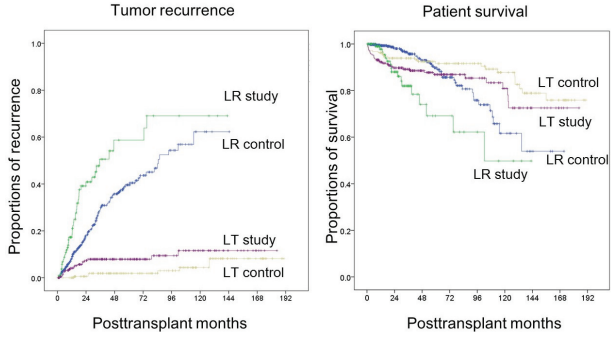

Figure 1. The tumor recurrence and patient survival curves in liver resection (LR) and liver transplantation (LT) study and control groups

recurrence was intrahepatic recurrence in both LR study and control groups, and extrahepatic metastasis in both LT study and control groups.

Conclusion: Patients achieving CPR after TACE followed by LT showed very favorable outcomes, which is comparable to those with minimal risk of recurrence. In contrast, following LR, down-staging effect from CPR was not definitely high and most tumors recurred at the remnant liver, thus strict surveillance is necessary as like in other HCC patients not showing CPR. These results would be reference data for studying the influence of widely variable degrees of pathological response after TACE in further clinical studies.

O - 085

Down-staging with Localized Concurrent Chemoradiotherapy Can Identify Optimal Surgical Candidates in Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Purpose: Locally advanced hepatocellular carcinoma (HCC) with portal vein tumor thrombosis is known to have a poor oncologic outcome. While the current standard of practice recommends only palliative treatments, many attempts with different modalities to increase survival have been undertaken. Primary goal of this study was to evaluate the oncologic outcome of surgical resection after down-staging with localized concurrent chemoradiotherapy (CCRT) followed by hepatic arterial infusion chemotherapy (HAIC) in locally advanced HCC with portal vein thrombosis.

Methods: From 2005 to 2014, 354 patients with locally advanced HCC underwent localized CCRT followed by HAIC. Among them, 149 patients with portal vein tumor thrombosis were analyzed. In order for an intention-to-treat analysis, exclusion criteria included total bilirubin ≥2mg/dL, platelet count <100000, and ICG R15 >20%. During the same study period, eighteen patients with portal vein tumor thrombosis underwent surgical resection as the first treatment modality. Clinicopathologic characteristics and oncologic outcomes between the groups were compared.

Results: With 51 patients in the exclusion criteria, 98 patients were finally analyzed in localized CCRT group. Among the 98 patients, 26 patients (26.5%) finally underwent curative resection. Clinicopathologic characteristic showed more frequent tumor thrombosis in the first order (81.6% vs. 22.2%, p<0.001) and bigger tumor size (9.0cm vs. 5.9cm, p=0.003) in localized CCRT group compared to the operation first group. Overall survival between the localized CCRT group and the operation first group, however, did not have a significant difference (median 13 months (95% CI: 10.10-15.90) vs. median 15 months (95% CI: 10.84-19.16), p=0.323). Further comparison of overall survival between the resection after localized CCRT group and the operation first group have shown significant difference (median 62 months (95% CI: 22.99-101.01) vs, median 15 months (95% CI: 10.84-19.16), p=0.006). Disease-free survival between these groups also revealed significant difference (median 32 months (95% CI: 3.47-60.54) vs, 3 months (95% CI: 2.03-3.97), p=0.002).

Conclusion: In HCC with portal vein thrombosis, patients who received resection after CCRT showed better overall and disease-free survival compared to those who received operation first. Localized CCRT can be a tool in identifying optimal surgical candidates in HCC with portal vein tumor thrombus

10. Basic, Cell Biology

June 18, 2016 | 13:50-15:30

O - 086

Activation of TRPC6 Channel Targeting Hepatic Stellate Cell Aggravates Liver Fibrosis

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Aims: Hepatic stellate cell (HSC) activation responded to injury is the major cause of hepatic fibrosis, activation of which has been linked with diverse Gaq-coupled receptors such as angiotensin II and endothelin-1 receptors. Gaq-coupled receptors are linked to phospholipase C-b activation leading to Ca2+ influx via TRPC channels. The Ca2+ signaling has been implicated either directly or indirectly in activation of HSCs causing de novo expression of a-smooth muscle actin (aSMA) and/or profibrotic ligand TGFb. However, the molecular identity and underlying mechanism of TRPC channels involving HSC activation remain unexplored.

Methods: To examine the molecular identity and underlying mechanism for TRPC channels involving hepatic fibrosis, we developed the hepatic fibrosis in vivo animal models using bile duct ligation and thioacetamide and HSC activation in vitro model using isolated primary HSCs. Transgenic overexpression of TRPC6 in mouse liver was performed using hydrodynamic gene delivery by tail vein.

Results: Notably, among TRPC sub-family, TRPC6 was a major Ca2+ influx mechanism in HSCs, and expression of which was significantly elevated in the hepatic fibrosis animal models and in activated HSCs. Fibrotic changes were ameliorated by inhibition targeting TRPC6 in fibrotic liver and activated HSCs in vitro and in vivo, respectively. Furthermore, transgenic overexpression of TRPC6 in mice induced de novo expression of aSMA supporting that TRPC6-mediated Ca2+ influx may involve in HSC activation leading to hepatic fibrosis.

Conclusions: Our data demonstrates that exaggerated expression and/or activity of TRPC6 initiates HSC activation and aggravates fibrotic changes. These results, thus, provide a new perspective on the pathogenesis of hepatic fibrosis and may provide clues for treating the cirrhosis. [This research was supported by NRF-2015R-1D1A1A01060454]

Keywords: TRPC6, Liver fibrosis, Ca2+ signaling, Hepatic stallate cell

O - 087

CXCL10 Is Produced in Hepatitis A Virus-infected Cells in an IRF3-dependent but IFN-independent Manner

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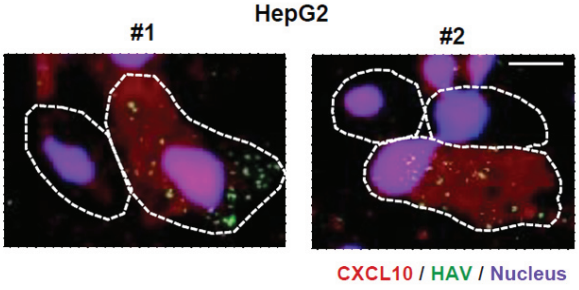
Aims: Acute hepatitis A (AHA) which is caused by hepatits A virus (HAV) infection is accompanied by severe liver injury in adult patients. In particular, CXCL10 recruits CXCR3-expressing T cells such as cytotoxic CD8+ T cells and helper 1 CD4+ T cells, therefore, contributes to liver injury. Although HAV is known to induce a minimal interferon (IFN) response in the infected liver, it strongly evokes the production of CXCL10 in the early stage of infection with unknown mechanisms. Herein, we investigated the mechanism how HAV infection induces the production of CXCR3 and CCR5 chemokines.

Methods: Primary human hepatocytes (PHHs) and HepG2 cells were infected with HM-175/18f HAV virus. To identify the signal pathways of chemokine production, silencing signal molecules downstream of RIG-I-like receptors or neutralization of secreted interferon (IFN) was performed. Eleven serum samples of AHA patients and those of healthy controls were collected, and CXCL10, CCL4, and CCL5 levels were determined.

Results: The production of CXCL10, CCL4 and CCL5 was markedly increased by HAV infection in the culture of PHHs and HepG2 cells. CXCL10 was induced in HAV-infected cells, not in neighboring uninfected cells. Moreover, these chemokines were significantly increased in the sera of acute hepatitis A patients. The production of IFN-λs was also robustly induced by HAV infection, and the blocking of secreted IFN-λs partially abrogated the production of CCL4 and CCL5 in HAV-infected cells. However, CXCL10 production was not decreased by the blocking of IFN-λ. Instead, CXCL10 production was reduced by silencing the expression of RIG-I-like receptor (RLR) signal molecules, such as mitochondrial antiviral signaling protein and interferon regulatory factor 3, in HAV-infected cells.

Conclusions: HAV infection strongly induces the production of helper 1 T cell-associated chemokines, particularly CXCL10 via RLR signaling, even without secreted IFNs.



Keywords: Hepatitis A virus, CXCL10, IRF3, IFN-λ

O - 088

Suppression of ADH3 Inhibit Hepatic Fibrogenesis by Modulating Cellular Interactions

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Aims: According to recent evidences, retinol and its metabolites are closely related with hepatic fibrogenesis. Especially, genetic ablation of alcohol dehydrogenase 3 (ADH3), a retinol metabolic gene that is expressed on hepatic stellate cells (HSCs) and natural killer (NK) cells, attenuated hepatic fibrogenesis in mice was suggested. Therefore, it has an importance whether pharmacological ablation of ADH3 has therapeutic effects on experimentally induced hepatic fibrosis in mice.

Methods: Hepatic fibrosis was induced by intraperitoneal injections of carbon tetrachloride (CCl4) or bile duct ligation (BDL) for two weeks. To inhibit ADH3-mediated retinol metabolism, 10 μg 4-methylpyrazole (4-MP)/g of body weight was administered to mice treated with CCl4 or subjected to BDL. The mice were sacrificed at week 2 to evaluate the regression of hepatic fibrosis. Liver tissue sections were stained for collagen and α-smooth muscle actin (α-SMA). In addition, HSCs and NK cells were isolated from control and treated mice livers for molecular and immunological studies.

Results: Administration of ADH3 inhibitor successfully inhibited CCl4- and BDL-induced hepatic fibrosis in mice, without any adverse effects. Especially, HSCs from 4-MP treated mice depicted decreased levels of retinoic acids and increased retinol contents than HSCs from control mice. In addition, the expression of α-SMA, transforming growth factor-β1 (TGF-β1) and type I collagen α1 was significantly reduced in the HSCs of 4-MP treated mice compared to the HSCs from control mice. Furthermore, inhibition of retinol metabolism by 4-MP increased interferon-γ production in NK cells, resulting in increased apoptosis of activated HSCs.

Conclusions: Based on our data, we conclude that inhibition of retinol metabolism by ADH3 inhibitor - 4-MP ameliorates hepatic fibrogenesis in mice through the activation of NK cells and suppression of HSCs. Therefore, in retinol and its metabolizing enzyme, ADH3, might be good therapeutic targets for the amelioration of hepatic fibrogenesis.

Keywords: Hepatic fibrogenesis, Hepatic stellate cell, Natural killer cell, Alcohol dehydrogenase III

O - 089

Granulocyte Colony Stimulating Factor Ameliorate Hepatic Apoptosis in Non-alcoholic Fatty Liver Disease via PI3K and AKT Activation: Beyond Marrow Stem Cell Mobilization

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Aims: Protective effects of granulocyte colony stimulating factor (G-CSF) on nonalcoholic fatty liver disease (NAFLD) have been reported in animal models. However, the therapeutic effect of G-CSF has been suggested via marrow stem cell mobilization. We investigated the direct effect of G-CSF on hepatocytes in NAFLD.
Methods: G-CSFr expression was evaluated in various liver disease model (NAFLD, alcoholic hepatitis, toxic hepatitis, chronic liver disease model). Two kinds of NAFLD models (high fat (HF), methionine choline deficient (MCD)) were used. In HF model included five arms as follows: control, HF, and three HF+G-CSF (30μg/kg, i.p) treatment groups (G1, G-CSF once weekly from 8th~12th week; G2, once daily for 5 days only in 9th week; G3, twice weekly from 9th to 12th week). In MCD model, four groups were included as follows; control, MCD, short and long acting G-CSF were tested. Long acting G-CSG was injected once a month. For in vitro experiments, the HepG2 cells were treated with palmitic acid (PA) 400μM, oleic acid (OA) 800μM, and G-CSF 100ng/ml. Cell viability (MTT) and oxidative stress (ROS), G-CSF receptor (IF, RT-PCR) were also measured.
Results: The G-CSFr expression increased significantly in HF (14.7 times), alcohol hepatitis (7.1 times), chronic thioacetamide (TAA) (2.4 times), and ischemia reperfusion (IR) (6.8 times) groups as compared to the control. In HF induced NAFLD model, G-CSF treatment did not decrease the body weight compared to control groups. Continuous low dose group which can't mobilize marrow stem cell (G3 group) showed significantly reduced intrahepatic fat accumulation as well as liver chemistry compare to HF induced NAFLD model without changing of body weight and liver to body weight ratio. Low dose long acting G-CSF with once a month injection also improved intrahepatic fat amount as well as degree of intrahepatic inflammation. Low dose long acting G-CSF treatment reduced the mRNA expression for hepatic de novo triglycerides synthesis (SREBP1c, FAS, SCD-1), cholesterol synthesis (SREBP2, HMG-CoA reductase) and inflammatory markers (MCP-1 TNF-a). G-CSF treatment increased cell proliferation markers (p-PI3 kinase, p-Akt), while decreased apoptosis in MCD diet groups. In Vitro results as follows; G-CSF+PA treatment increased cell viability in both 24h, and 48h treated groups. ROS was also significantly reduced in G-CSF group. Cell viability increased G-CSF group but decreased in G-CSF+PI3 kinase inhibitor and PI3 kinase inhibitor alone groups. Similarly, ROS decreased G-CSF but increased in G-CSF+PI3 kinase inhibitor and PI3 kinase inhibitor alone groups.
Conclusions: G-CSF receptor expression in Hepatocytes in various NAFLD model and G-CSF administration of low-density low-frequency improves HF model and long acting G-CSF improves MCD model.
Keywords: NAFLD, G-CSF, G-CSF receptor, PI3 kinase

O - 090

Human Placenta-Derived Mesenchymal Stem Cells Restore Hepatic Lipid Metabolism in the Rat Bile Duct Ligation Model

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Aims: Mesenchymal stem cell (MSC) transplantation was determined to promote hepatic regeneration and reduce liver fibrosis. However, the influence of MSCs on hepatic lipid metabolism is not yet elucidated. We transplanted human placenta-derived mesenchymal stem cells (PD-MSCs) in bile duct-ligated rats to investigate whether alterations in lipid metabolism are restored.
Methods: Serum biochemical analysis and histological evaluation of liver were performed. The expression levels of enzymes involved in hepatic lipid metabolism were examined by quantitative real-time polymerase chain reaction analysis, immunoblot analysis, or quantitative enzyme-linked immunosorbant assay (ELISA) analysis.
Results: Bile duct proliferation and periductal inflammation were reduced by PD-MSCs transplantation. Elevation of serum levels of total bilirubin and alkaline phosphatase was attenuated in the transplanted rats. Moreover, serum lipid levels decreased, mainly in the fraction of low-density lipoprotein cholesterol and triglyceride. Fatty acyl-CoA synthetase concentrations measured by ELISA in liver tissues increased following PD-MSC transplantation, and the mRNA levels of long-chain acyl-CoA synthetase 1 and fatty acid transport protein 2 were also elevated. Whereas mitochondrial carnitine palmitoyltransferase 1a (CPT1a), a rate-limiting enzyme in the mitochondrial β-oxidation, expression at the mRNA level was augmented in the transplanted rats, its protein expression was suppressed. The expression levels of microRNA-33 (miR-33), which has been shown to posttranscriptionally regulate genes involved in fatty acid oxidation, were markedly higher in the transplanted rats, indicating that CPT1a expression is repressed by miR-33.
Conclusions: These results suggest that the transplantation of PD-MSCs restores altered hepatic lipid metabolism in bile duct-ligated rats.
Keywords: Mesenchymal stem cells, Placenta-derived mesenchymal stem cells, Lipid metabolism, Mitochondrial β-oxidation

O - 091

Exosome Derived from Palmitic Acid-treated Hepatocytes Activates Hepatic Stellate Cells

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Aims: Although nonalcoholic fatty liver disease (NAFLD) is becoming dominant cause of chronic liver disease, the exact mechanism of progression from simple steatosis to nonalcoholic steatohepatitis (NASH) have yet to be elucidated. We aimed to investigate the role of exosome from lipid laden hepatocyte in the context of NAFLD

progression in vitro.
Methods: We isolated exosome from human hepatoma cell lines (Huh7 or HepG2) treated with palmitic acid (PA). Concentration of exosome was determined with exosome quantitation assay kit. LX-2 cells, human hepatic stellate cell (HSC) line, were treated with isolated exosome from PA treated cells. Fibrosis marker including transforming growth factor beta1 (TGF-b1), alpha-smooth muscle actin (a-SMA) and collagen type 1 alpha 1 (Col1a1) expression were measured.
Results: Compare with controls, PA-treated hepatocytes significantly increased CD36 and exosome production (8.6 vs. 5.5 X 10^7 /μL, p <0.01). When LX-2 cells were cultured with exosome from hepatocytes, TGF-β1, α-SMA, and Col1a1 expression in LX-2 cells were significantly increased compared to control. Moreover, exosome from PA-treated hepatocytes more increased the expression levels of fibrosis markers. High concentration of exosome (100 μg/mL) more increased the expression levels of fibrosis markers compared to low concentration of exosome (50 μg/mL).
Conclusions: Palmitic acid treatment enhanced the production of exosome in hepatocytes. Exosomes derived from palmitic acid-treated hepatocytes increased expression levels of fibrotic genes in HSCs. Therefore, exosome might have important roles for crosstalk between hepatocytes and HSCs in the progression to NASH from simple steatosis.
Keywords: Exosome, NASH, NAFLD

O - 092

Activating Transcription Factor 3 Is a Targeted Molecule Linking Hepatic Steatosis to Type 2 Diabetes

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Aims: Nonalcoholic fatty liver disease (NAFLD) contributes to the induction of impaired glucose tolerance leading to the development of type 2 diabetes mellitus (T2D); however, the precise mechanism by which hepatic steatosis may induce T2D remains unclear.
Methods: Zucker diabetic fatty (ZDF) rats (6 and 19-week) and Zucker lean (ZL) control rats were used for animal studies. We used an in vivo-jetPEI siRNA delivery system to clarify the functional role of activating transcription factor 3 (ATF3) in the progression of hepatic steatosis to T2D. We analyzed the baseline cross-sectional data derived from the NAFLD registry cohort (NCT02206841; n=322) of Seoul National University Boramae Medical Center.
Results: We demonstrated that ATF3 was highly expressed in the liver of ZDF rats and human subjects with NAFLD and/or T2D. Insulin resistance and hepatic steatosis were associated with increased ATF3 expression and decreased fatty acid oxidation through mitochondrial dysfunction, which were attenuated by in vivo-ATF3 silencing. Knockdown of ATF3 also ameliorated glucose intolerance, impaired insulin action, and inflammatory responses in ZDF rats. In human subjects with NAFLD and/or T2D, a significant positive correlation was noticed between hepatic ATF3 expression, surrogate markers of T2D, mitochondrial dysfunction, and macrophage infiltration.
Conclusions: In conclusion, hepatic overexpression of ATF3 is closely associated with hepatic steatosis and incidental T2D and thus ATF3 may serve as a potential therapeutic target for NAFLD and hepatic steatosis-induced T2D.
Keywords: Activating transcription factor, Endoplasmic reticulum stress, Mitochondria, Macrophage

O - 093

The Inhibitory Effect of Lorcaserin on Non Alcoholic Fatty Liver Disease in Animal Model

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Aims: Nonalcoholic fatty liver disease (NAFLD) is characterized by a wide spectrum of liver damage spanning steatosis, nonalcoholic steatohepatitis, and liver cirrhosis. The aim of this study is to investigate the efficacy of lorcaserin on NAFLD in animal model.
Methods: The leptin receptor deficient db/db mice and control mice (db/m) were fed a diet deficient in methionine and choline (MCD diet) and control diet for 8, respectively. Twenty mice were divided into 3 groups. The first group was fed a control diet without treatment and referred as the control group. The second group was administered with MCD diet +0.7% DMSO. The third group was administered with MCD diet +0.7% DMSO +5mg/ml of lorcaserin. Change of body weight was observed and blood was collected before sacrifice. After being sacrificed, the liver tissues were collected and fixed in formalin. Histological evaluation was evaluated by blindly pathologist.
Results: The body weight of control mice was increased during the study, whereas feeding db/db mice MCD diets for 8 weeks significantly reduced in body weight. Lorcaserin treated group was associated with more rapid body weight loss compared with DMSO-treated controls. MCD diet induced excessive fat accumulation, inflammation, and some fibrosis. Liver enzyme and triglyceride were improved in lorcaserin-treated group compared with DMSO-treated control (DMSO vs lorcaserin: AST 411.3 ±40.26 vs 304.7 ±28.88 (U/L), ALT 544.8 ±38.7 vs 434.5 ±29.68 (U/L), triglyceride 31.8 ±2.02 vs 26 ±1.58 (mg/dL)). Liver histopathology showed that the fat accumulation and inflammatory cell infiltration were decreased in MCD diet +lorcaserin-treated mice compared with MCD diet +DMSO-treated controls.
Conclusions: These results showed beneficial effects of lorcaserin against excessive fat accumulation and inflammation as well as liver enzyme. Therefore, our findings indicate that lorcaserin could be contributing to the decline of progression of nonalcoholic fatty liver disease.
Keywords: Non-alcoholic fatty liver disease, NASH, Lorcaserin, NAFLD animal model

O - 094

HNF4α as Therapeutic Agents for Non-alcoholic Fatty Liver Disease Changing with Bile Acid Metabolism

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Aims: Hepatocyte nuclear factor 4α (HNF4α) is known as a master regulator of liver-specific gene expression. The effects of HNF4α on non-alcohol fatty liver disease (NAFLD) are largely unknown. In this study, we evaluated the role of HNF4α in NAFLD.

Methods: Biopsy proven 52 NAFLD liver samples, and two different NAFLD animal models (high fat and MCD model) were used for evaluating expression of hepatic HNF4α. HepG2 cells were co-treated with palmatic acid (PA) and/or chenodeoxycholic acid (CDCA) for 24 hours. HNF4α was over-expressed using microporator in HepG2 cells. HNF4α was down-regulated using siRNA system. After transfection, MTT assay, Nile-red staining, and qPCR genes for lipid and bile acid pathways were evaluated.

Results: HNF4α expression was increased in human, and MCD model. HNF4α overexpression increased fatty oxidation (ACOX1, and CPT1A), and VLDL secretion pathway (MTTP, and ApoB) in HepG2 cell. But palmitic acid treatment decreased HNF4α expression in HepG2 cells. And HNF4α overexpression attenuated palmitic acid induced hepatic apoptosis as well as intrahepatic fat accumulation. However, not only fatty acid metabolism but also bile acid metabolism was changed in NAFLD model. SHP and NTCP expression were decreased, and CYP7A1 expression was increased in MCD animal model. Interestingly, palmatic acid and CDCA co-treatment also increased HNF4α mRNA expression in HepG2 cells; however, each treatment alone did not affect the HNF4α mRNA expression. HepG2 cells with siRNA induced down regulation of HNF4α were protected against bile acid-induced toxicity. HNF4α down-regulation also exhibited decreased mRNA expression of bile acid transporter (NTCP) and bile acid synthesis (CYP7a1) enzymes.

Conclusions: HNF4α attenuates hepatic injury by decreasing bile acid synthesis and bile acid uptake in NAFLD model.

Keywords: NAFLD, HNF4a, Bile-toxicity, Lipotoxicity

O - 095

The Combined Effect of Stem Cell Factor and Granulocyte Macrophage Colony-stimulating Factor Administration after 90% Partial Hepatectomy in Rats

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Aims: The purpose of this study was to identify the impact of exogenous SCF and GM-CSF administration after 90% major hepatectomy in rats.

Methods: Sprague Dawley rats underwent 90% major hepatectomy using a bile duct-sparing portal pedicle ligation technique under microscopy. The rats were divided into two groups: group 1 (phosphate-buffered saline) and group 2 (SCF+GM-CSF treatment, each 25 mcg/kg). Treatment was administrated immediately after operation through the inferior vena cava. Liver regeneration capacity and expression of cytokines and their downstream signaling molecules were evaluated at postoperative day 1, 2, 4, and 7.

Results: The survival rate after 90% hepatectomy in rats using this technique were increased to 95% compared with 55% with conventional parenchymal ligation technique ($p = 0.004$). The combination effect of SCF and GM-CSF was evaluated in in vitro study. Group 2 exhibited a significantly increased liver regeneration index at early period after hepatectomy compared to group 1 (day 2: 287.5 ± 19.6 vs. 513.9 ± 67.1, $p = 0.025$ and day 4: 647.6 ± 108.8 vs. 941.7 ± 53.9, $p = 0.046$). Furthermore, serum liver enzyme levels including total bilirubin, aspartate aminotransferase, and alanine aminotransferase, were significantly lower in group 2 than in group 1 on postoperative days. The expression of Ki-67 and cyclin D1 were significantly higher in group 2 than in group 1 on postoperative days. Group 2 displayed significant increases of interleukin (IL)-6 and transforming growth factor (TGF)-β expression within 24 h after hepatectomy. Especially, C-X-C motif chemokine 12 (CXCL12)/C-X-C chemokine receptor type 4 (CXCR4) and matrix metalloproteinases 2 and 9 levels in the liver tissue of group 2 were also significantly upregulated according to quantitative polymerase chain reaction on postoperative days.

Conclusions: Our data suggest that the administration of SCF+GM-CSF after major hepatectomy can enhance liver regeneration by liver cell proliferation and mobilization of stem cell modulating IL-6/TGF- β and CXCL12/CXCR4 pathway as well as by matrix remodeling. These findings suggest the possibility of therapeutic treatment using a combination of SCF and GM-CSF in the clinical setting to promote liver regeneration after extreme hepatectomy.

Keywords: Liver regeneration, SCF, GM-CSF, Partial hepatectomy

11. Surgery

June 18, 2016 | 16:30-17:40

O - 096

Extrahepatic Glissonean Pedicle Approach in Laparoscopic Anatomical Liver Resection : A Single Institutional Early Experience

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Purpose: Laparoscopic anatomical liver resection still present s major technical difficulties, such as pedicle control. The extrahepatic glissonean pedicle approach has the advantages of less intraoperative bleeding, shorter operative time, and better oncological outcomes in our and other previous studies. We here review our early experience with laparoscopic anatomical liver resection by using extrahepatic glissonean pedicle control.
Methods: We retrospectively reviewed the records of 12 patients who underwent laparoscopic anatomical liver resection through extrahepatic glissonean pedicle approach at Hallym University Sacred Heart Hospital of Korea, between May 2015 and February 2016. After laparoscopic extrahepatic glissonean pedicle control, liver mobilization and parenchymal transection were done by Harmonic scalpel and CUSA.
Results: There were 12 patients in this study. In the present study, anatomical resection included the followings: monosegmentectomy in 3 patients, left lateral sectionectomy in 2 patients, left medial sectionectomy in 1 patient, left hepatectomy in 2 patients, right anterior sectionectomy in 1 patient, right posterior sectionectomy in 3 patients. The mean age was 56.00 years, mean operation times : 205.42 min, mean blood loss : 700 ml. The mean hospital stay was 8.67 days. The mean tumor size was 3.4cm. All resection margin was negative. Conversion rate was 8.33% (only one case). Overall morbidity was 8.33% and overall mortality rate was 0%.
Conclusion: Laparoscopic anatomical liver resection by using extrahepatic glissonean pedicle approach appears to be both feasible and safe for the performance of laparoscopic major liver resection. The Results of current study show the results in terms of early recovery period. Although, our experience shows that oncologic outcomes are acceptable in terms of margin, further study to evaluate for long-term safety is needed.

O - 097

Totally Laparoscopic Right Hepatectomy in HCC Patients with Portal Vein Anomaly

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Purpose: Laparoscopic right hepatectomy was a challenging procedure, but has been gradually changed to standard approach. Glissonian pedicle approach for hepatic inflow control has been mainly used in laparoscopic right hepatectomy because of the difficulty of separate dissection of portal vein, hepatic artery and bile duct. However, the exact glissonian pedicle approach on laparoscopic field is more difficult procedure in patients with portal vein anomaly. Such an inappropriate hepatic inflow control induces unexpected blood loss and inaccurate hepatic parenchymal transection and especially, the complication risk of left portal vein and the injury risk of hepatic duct may be increased in patients with portal vein anomaly.
Methods: We performed totally laparoscopic right hepatectomy in 3 patients with type II or III portal vein anomaly by individual hepatic inflow dissection.
Results: After ligation of right hepatic artery, the meticulous dissection of right posterior and anterior portal vein was performed and the inflow control can be accomplished by the clipping or ligation along with the confirmation of portal vein anomaly. In order to avoid the injury of hepatic duct, the remnant right anterior and posterior portal pedicles were respectively ligated at the distal site of separate portal vein clamping after the completion of liver parenchymal dissection. Postoperative imaging study illustrated the exact transection of portal tract.
Conclusion: In summary, totally laparoscopic right hepatectomy in patients with portal vein anomaly is not feasible and safe procedure without the complete dissection of right portal tract. Therefore, the inflow control by separate portal vein dissection is more useful option than blunt hepatic glissonian pedicle approach for prevention of portal tract injury in our opinion.

O - 098

Comparative Short-term Outcomes of Laparoscopic Anatomical Liver Resection for the Centrally Located Tumor: Case-matched Study with Propensity Score Matching

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Aims: Recent advanced technology and an accumulation experience of surgeons have expanded the indications for laparoscopic liver resection. However, compared with open liver resection, laparoscopic anatomical liver resection for centrally located tumor has not been well established in terms of feasibility. The aim of our study was to assess the feasibility and safety of laparoscopic anatomical major liver resection for the centrally located tumor.
Methods: From September 2005 to April 2015, 138 consecutive anatomical major liver resections for the centrally located tumor such as central hepatectomy (CH) and right anterior sectionectomy (RAS) were performed, including 14 cases of totally laparoscopic anatomical liver resections. In order to compensate the selection bias, we performed one or/and up to five match using propensity score matching between laparoscopic and open liver resection.
Results: After propensity score matching, 14 and 39 patients were included in the Laparoscopic liver resection (LLR) and Open liver resection (OLR) group, respectively. Surgical time was longer in the LLR group (393, range 131 to 661 minutes) than the OLR group (270, range 92 to 500 minutes) ($p = 0.001$), but the hospitalization was shorter (8, range 5 to 24 days versus 11, range 5 to 183 days, $p = 0.061$). The portal triad clamping time was shorter (15 versus 25 minutes, $p = 0.833$) and mean blood loss was less in LLR (471 versus 489 mL, $p = 0.603$) but the values were not statistically significant. The morbidity rates were 36% (5 of 14 cases) in the LLR group and 28% (11 of 39 cases) in the OLR group. There was no postoperative mortality in either group.

Conclusions: Laparoscopic approach for CLT requiring CH or RAS seems feasible with non-inferior outcome perioperative compared to OLR. CLT may be performed safely by totally laparoscopic approach in experienced hands.

Keywords: Laparoscopic liver resection, Centrally located liver tumor, Central hepatectomy, Propensity score matching

O - 099

Prospective Randomize Control Study of Clinical Usefulness of Prophylactic Antibiotics Therapy in Laparoscopic Cholecystectomy

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Purpose: Laparoscopic cholecystectomy (LCC) is the procedure of generating a low infection ratio, the role of prophylactic antibiotics are debatable. We evaluated the usefulness of prophylactic antibiotics during elective LCC.

Methods: 508 patients performed elective LCC at Chonbuk National University Hospital between April 2014 and December 2015. They were randomized studied by comparing with antibiotic group (n=249, AG, cefotetan 1g, 1 dose/prophylactic) and non-antibiotic group (n=260, NAG) by table of random numbers. The clinical variables were pre and post-operatively blood tests including WBC, ESR, CRP, body temperatures, symptoms and imaging of chest x-ray to evaluate the infections.

Results: There were no significant differences in clinical characteristics between the two groups. [AG (M:F=103:146, mean age : 51.1±14.4 years, mean BMI 25.2±3.8 kg/m2) and NAG (M:F=109:151, mean age : 51.2±14.5 years, mean BMI 24.9±3.5 kg/m2); p>0.05]Eight of NAG (3%) and two (0.8%) of AG were fever (≥38℃) at 2nd post-operative day (POD). 52 of NAG (20%) and 40 (16%) of AG were leukocytosis (≥12,000/mm3) during 14th POD. One of both group had fluid collection on abdomen CT but no growth in culture. And two patient of NAG (0.7%) had a serous wound discharge during 14th POD, also bacteria were not identified. There was no significant difference between the two groups in comparison of factors to suspect infection such as fever (≥38℃), leukocytosis (≥12,000/mm3), elevation of ESR (≥9mm/hr) and CRP (≥5mg/L). And there was no variable that affected factors to suspect infection in the multivariate analysis.

Conclusion: In our results, prophylactic antibiotics are no significant differences in both groups during LCC. Therefore, it is not necessary to use prophylactic antibiotics during elective LCC in patients of including criteria.

O - 100

Outcome of Transduodenal Surgical Ampullectomy for Ampullary Neoplasms

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Purpose: Adenomas arising from the ampulla of Vater (AoV) are premalignant lesions with risk for malignant transformation to carcinoma following the adenoma-to-carcinoma sequence. Accordingly, many experts advocate resection either endoscopically or surgically. However, excluding associated malignant disease prior to resection of an adenoma of the AoV is not always possible. And the procedure of choice to treat this rare tumor is still controversial among endoscopic papillectomy (EP), transduodenal surgical ampullectomy (TSA) and pancreatoduodenectomy (PD). With the introduction of EP recent years, TSA was regarded as a tool for unsuitable lesion for EP or after unsuccessful EP by some. In addition to this there might be a role of TSA for preinvasive early stage adenocarcinoma of AoV, substituting PD. This study was done to evaluate the outcomes of transduodenal surgical ampullectomy (TSA) of ampulla of Vater (AoV) neoplasm including adenoma as well as adenocarcinoma limited to the ampulla.

Methods: 22 cases of AoV neoplasm treated by transduodenal surgical ampullectomy (TSA) during the period from 2010 to 2015 were reviewed retrospectively.

Results: The patients were aged from 36 to 81 years (mean 56) and 12 were male. 11 patients were identified during routine health screening. The most frequent symptom was indigestion and noted in 4. Cholangitis and liver abscess was the initial presentation in one case each. Two cases were associated with familial adenomatous polyposis syndrome (FAP). Seven cases of TSA were performed after endoscopic papillectomy for unsuitability (2), inadequacy (2) or tumor recurrence (3). Preoperative endoscopic biopsy revealed adenoma in 11, low grade dysplasia (LGD) in 4, high grade dysplasia (HGD) in 5 and neuroendocrine tumor in 1. No case was diagnosed as adenocarcinoma on preoperative biopsy. Intraoperative frozen biopsy was done in 14 cases and revealed adenocarcinoma in 4 which were corresponding to adenoma in 2, LGD in 1 and HGD in 1 on preoperative biopsy. Two patients were converted to pylorus preserving PD according to the frozen biopsy result. Of TSA, 100 per cent had clear margins grossly and microscopically. Postoperative pathology revealed adenocarcinoma in 7 cases. All the adenocarcinomas were in their very early stage, reflected by carcinoma in situ in 2, invasion to lamina propria in 2, confined to mucosa in 1, confined to ampulla of Vater in 1 and focal adenocarcinoma of 2mm. There was no case of lymphovascular or perineural invasion. And those 2 cases who underwent PPPD revealed no lymph node metastasis. 5 patients with adenocarcinoma who underwent TSA showed no evidence of recurrence during follow period from 22 to 58 months. And all the 13 patients with adenoma, either with or without HGD showed no

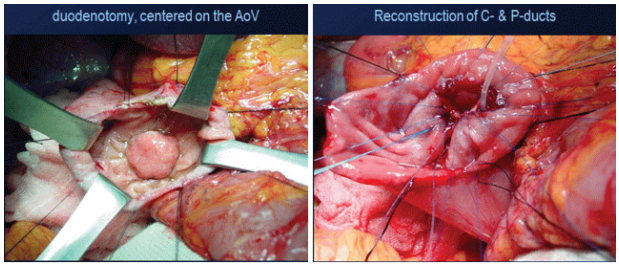

Figure 1. Intraoperative view of transduodenal surgical ampullectomy.

evidence of recurrence for 2 to 69 months. There were 3 complications after TSA including wound seroma in 1, voiding difficulty in 1 and T inversion on EKG in 1.

Conclusion: Transduodenal surgical ampullectomy can be done safely with minimal morbidity while securing adequate safety margin for ampullary neoplasm. When the preoperative biopsy result of ampullary neoplasm does not tell adenocarcinoma definitely, TSA would be a good substitute for PD even though preoperative biopsy was not always correct in detecting adenocarcinoma. More study to define the detailed indication of TSA for adenocarcinoma of AoV is needed.

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Attenuated Role of Neoadjuvant Concurrent Chemoradiotherapy in Resectable Uncinate Process Pancreatic Cancer

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Purpose: Uncinate process pancreatic cancer (UPC) is usually discovered in a relatively advanced stage. However, neoadjuvant concurrent chemoradiotherapy (CCRT) followed by pancreatoduodenectomy (PD) in UPC have shown comparable oncologic outcome with that of usual pancreatic head cancer (PHC). This study aimed to evaluate oncologic outcome of resectable UPC and determine whether neoadjuvant CCRT is truly necessary.

Methods: A retrospective analysis of 204 patients with resected pancreatic head cancer at a single center from Jan. 2005 to Dec. 2014 was conducted. Clinicopathologic characteristics and oncologic outcomes of resectable UPC and resectable PHC were analyzed.

Results: Among 41 patients diagnosed with resectable UPC, 14 (34.1%) patients received neoadjuvant CCRT, whereas 27 (65.9%) patients received operation first. Overall survival between surgery first and neoadjuvant CCRT did not have significant difference (p=0.341, mean survival 32 months vs. 18 months, respectively). During the same period, there were 90 patients diagnosed with resectable PHC. Survival outcomes between resectable UPC and resectable PHC were similar, with median survival of 26 and 20 months, respectively (p=0.427).

Conclusion: UPC was recommended for neoadjuvant CCRT from a previous study. However, our analysis suggests that neoadjuvant CCRT may not have a significant role in resectable UPC and surgery should be recommended as a first option.

12. Liver Cirrhosis, HCC

June 18, 2016 | 16:30-17:40

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The Prevalence of Osteoporosis in Alcoholic Cirrhotic Patients : A Multicenter Study in Gangwon Province, South Korea

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Aims: Although osteoporosis in alcoholic liver cirrhosis (ALC) is clinically important because of resulting a significant morbidity such as spinal fractures, its real prevalence in Korea remains unknown. The aim of this prospective study is to describe the prevalence of osteopenia and osteoporosis assessed by the reference method. In addition, another aim of this study is to identify affecting factors on osteoporosis in ALC patients.

Methods: We present the prospective multicenter study. During July 2013 to March 2015, one hundred eight ALC patients who admitted at four centers in Gangwon province were consecutively recruited. The diagnosis of osteoporosis and osteopenia in ALC is made after a bone densitometry by WHO criteria. Alcohol consumption habits, known risk factors of osteoporosis development through lifestyle questionnaires, laboratory findings, and hormone levels were also conducted.

Results: The crude prevalence of osteoporosis in ALC patient (29-82 years old) was 20.0% for men (N=95) and 15.4% for women (N=13). Our data compared with that of 2008-10 Korean National Health and Nutrition Examination Survey data, the prevalence of osteoporosis in ALC patient(male, >50 years) was high (20.0% vs. 7.8%). The free testosterone level (1.93±1.80 pg/mL vs. 4.24±2.81 pg/mL; P=0.007) and trabecular bone score; an index of bone microarchitecture (1.08±0.13 vs. 1.25±0.15; P=0.001) were significantly lower in osteoporosis in ALC patients. The intact PTH (45.07±28.10 pg/mL vs. 29.50±17.53 pg/mL; P=0.014) and PT(INR) (1.44±0.37 vs. 1.26±0.20; P=0.018) were higher in patients with osteoporosis.

Conclusions: Our data shows high prevalence of osteoporosis in alcoholic cirrhosis patients than healthy Koreans, as we expected. This finding highlights the need for prophylactic measures to optimize bone health in patient with alcoholic liver cirrhosis.

Keywords: Ver Cirrhosis, Alcoholic, Osteoporosis, Bone density

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Changes in the Cardiac Varices after Eradication of Esophageal Varices by Band Ligation

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Aims: Esophageal varices (EVs) is a common complication of liver cirrhosis. In many cases, esophageal varices extends to the cardia to form gastroesophageal varices type 1 (GOV1). Practice guidelines recommends treatment for EVs only because previous stud-

ies suggested that cardiac varices (CVs) are usually disappeared with eradication of EVs. However, most of the supporting data were results of the esophageal injection therapy (EIS), not endoscopic band ligation (EBL). This study was performed to evaluate the effect of EV eradication by EBL on the CVs.

Methods: Cirrhotic patients who achieved eradication of EVs by EBL were included. Patients who were treated with EIS, received endoscopic therapy for CVs, or combined with hepatocellular carcinoma were excluded.

Results: Ninety-seven patients with EV eradication by EBL were enrolled. Age was 59.3 years and 79 patients (81.4%) were men. Initial purposes of EBL were primary prophylaxis in 56 patients, management of acute variceal bleeding and secondary prophylaxis in 41 patients. EV eradications were achieved with 7.8±4.4 bands in 2.5±1.3 sessions during 2.7±1.5 months. After EV eradication, CVs were disappeared, decreased, or unchanged in 59 (60.8%), 22 (22.7%), and 16 (16.5%) patients, respectively. Although CV disappearance was not related with the size of EVs or EVs at baseline, there was a tendency of increased rates of CV disappearances in CVs on lesser curvature than those on greater curvature (63.3% vs 28.6%, P=0.070). During follow-up, EVs recurred in 39 patients with recurrence rates at 1, 2, and 3 years of 19.0%, 35.7%, and 48.6%, respectively. Recurrence of EVs was more frequent in patients with remained CVs than those with disappeared CV after EV eradication (P=0.018).

Conclusions: CV was frequently disappeared with eradication of EVs by EBL in patients with GOV1. Remained CVs after EV eradication was associated with earlier recurrence of EVs after EV eradication by EBL.

Keywords: Liver cirrhosis, Cardiac varices, Endoscopic band ligation

O - 104

Effects of Splanchnic Vasoactive Agents on Hepatic Functional Recovery and Regeneration in Porcine 70% Partial Hepatectomy Model

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Aims: Excessive portal pressure is considered as one of the most important factor for development of post-hepatectomy liver failure (PHLF) and small-for-size syndrome (SFSS) after partial liver transplantation. We aimed to determine the effects of splanchnic vasoactive agents such as terlipressin and octreotide on recovery of hepatic function and regeneration using porcine 70% hepatectomy model, for evaluation of potential for clinical use in prevention and treatment of PHLF and SFSS.

Methods: Twenty-one pigs were divided into 4 groups; sham operation group (n = 3), control group (n = 6), terlipressin group (n = 6) and octreotide group (n = 6). 18 pigs except sham operation group underwent 70% hepatectomy. Terlipressin (0.5mg, t.i.d.) and octreotide (0.5mg, t.i.d.) were administered via subcutaneous route starting immediately after completion of hepatectomy. Portal pressure was measured at baseline, 0.5, 1, 6 hours and 7 days after hepatectomy. Blood samples were drawn at baseline, 1,6 hours and 7 days after hepatectomy for measurement of aspartate aminotransferase, bilirubin, prothrombin time. Animals were executed on 7th day from initial hepatectomy. 7-day survival rate was calculated and histologic scoring of liver injury was measured.

Results: Portal pressure was significantly lower in terlipressin and octreotide group than control group (p = 0.009 and 0.034, respectively). None in octreotide group, one in terlipressin group and two in control group expired before planned termination on 7th day Mean survival time was not significantly different between groups (p = 0.301). Asparate aminotransferase was significantly lower in terlipressin group than control group (p = 0.021) and total bilirubin was also lower in terlipressin group than control group with borderline significance (p = 0.083). Liver regeneration rate was significantly lower in terlipressin group than control group (p = 0.032). Histologic scoring focusing on inflammatory change was decreased in both treated groups than control group (terlipressin group; p = 0.014, octreotide group; p = 0.056).

Conclusions: Splanchnic vasoactive agents, especially terlipressin decreased portal pressure and showed better clinical features despite of lower liver regeneration rate after liver resection. It indicates that these drugs may play an important role in prevention and treatment of PHLF and SFSS maintaining a balance between liver regeneration and functional recovery.

Keywords: Post-hepatectomy liver failure, Small-for-size syndrome, Terlipressin, Octreotide

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Hemorheological Alteration in Patients Clinically Diagnosed with Chronic Liver Diseases

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Aims: Blood viscosity is predominantly determined by hematocrit, plasma viscosity, and the aggregation of red blood cells. We investigated the level of whole blood viscosity in patients with chronic liver diseases (CLD).

Methods: A total of 320 patients whose whole blood viscosity (WBV) had been measured between August 2015 and April 2016 at Seoul St. Mary's Hospital were retrospectively reviewed. Plasma WBV was measured using a scanning capillary tube viscometer at a high shear rate (systolic) and a low shear rate (diastolic). Among them, 151 patients were clinically diagnosed with CLD based on clinical in-

Table 1. Comparison of WBV by liver parenchymal status

	Reference	Fatty liver (n=46)	Chronic hepatits (n=70)	Liver cirrhosis (n=35)
WBV (cP)				
Systolic	4.03 (3.4-5.2)	5.25 ± 1.01	5.03 ± 0.89	4.44 ± 0.83
Diastolic	10.63 (8.3-14.3)	16.65 ± 3.78	15.98 ± 3.23	13.81 ± 3.30

* WBV: whole blood viscosity

formation and imaging study. We investigated the CBC, blood chemistry, and lipid profiles of these patients. Reference values for whole blood viscosity of normal controls were adapted from a previous report (Jung et al. Clinical Biochemistry 2014;47:489-493).

Results: Chronic liver diseases were categorized into 3 groups : fatty liver (n=46), chronic hepatitis (n=70) and liver cirrhosis (n=35). Systolic blood viscosities (SBV) of plasma whole blood viscosity were 5.25 centipoise (cP), 5.03cP, 4.44cP in fatty liver, chronic hepatitis and liver cirrhosis, respectively. Diastolic blood viscosities (DBV) were 16.65 cP, 15.98 cP, 13.81 cP in fatty liver, chronic hepatitis and liver cirrhosis, respectively. These results indicated that the levels of blood viscosity were increased in CLD compared with healthy control. Regarding the blood viscosity according to the etiology of CLD, those were significantly lower in HBV- and HCV-related CLDs than NAFLD and alcoholic liver disease. Among CLDs, the level of the WBV in liver cirrhosis was the lowest ($P<0.05$).

Conclusions: The level of whole blood viscosity of patients with chronic liver diseases was higher than that of normal controls. These result suggest that blood viscosity test may be useful tool to predict the prognosis of chronic liver diseases.

Keywords: Blood viscosity, Chronic liver disease, Capillary Tube Viscometer

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Generation of 3D Hepatic Structure Using Induced Hepatocyte-like Cells Directly Converted from Fibroblasts

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Purpose: To deal with the liver failure at the end stage, liver transplantation is ultimately the only treatment at the terminal stages of disease. However, the demand for liver transplantation is more than number of provision cadaveric livers or liver tissues from living donors. Hence, developing the way of acquiring hepatocytes has been considered as an important researching issue for decades. In recent, direct conversion technology has been developed for generating induced hepatocyte-like cells (iHeps) through ectopically expressing liver-specific transcription factors. On the other hands, tissue-engineering including '3-dimensional (3D) bioprinting technology' has been advanced for organ-like structures and thereby capturing the complexity of in vivo environments. Therefore, we herein report the reconstruction of 3D bioprinted hepatic architecture for recapitulating the microenvironment in liver by using the iHeps as a source of hepatocytes.

Methods: To generate iHeps, mouse embryonic fibroblasts (5x104 cells) were transduced with pMX retroviruses expressing individual hepatic transcription factors, Hnf4a and Foxa3. After 48 h, the cells were further cultured in hepatocyte culture medium (HCM) on Type I collagen-coated dish for inducing lineage transition toward iHeps. For 3D bioprinting, the iHeps encapsulated with 3% alginate hydrogel, and then extruded through nozzle pressure. After crosslinking with calcium chloride, hepatic structure was formed with 25x25mm.

Results: After 8~10 days of transduction, we observed epithelial iHep colonies with high proliferation rate. Upon several passaging, the number of the fibroblasts was reduced, while the iHeps grew dominant on the dish. Both qPCR and immunofluorescence analyses revealed that iHeps shared typical hepatic gene and protein expression profiles with liver tissue. Moreover, iHeps also had functional characteristics as hepatocytes such as glycogen storages and xenobiotic activity. Through 3D bioprinting method, we can efficiently construct multiple layered-3D hepatic structures. Interestingly, we found that mimicking the 3D hepatic structure not only assists the iHeps to stably repopulate, but also enhanced hepatic gene expression profiles of iHeps.

Conclusion: Combining 3D bioprinting technology with iHep generation protocol may be a realistic option for overcoming the problems including donor shortage and surgical complications of liver transplantation, and thereby offers a new paradigm in the field of liver regenerative medicine.

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Evaluation of Safe Guideline to Prevent Posthepatectomy Liver Failure after Right Hepatectomy for Hepatocellular Carcinoma

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Purpose: It is well known that the degrees of liver fibrosis, portal hypertension, residual liver volume are crucial factors for posthepatectomy liver failure (PHLF) in the hepatocellular carcinoma (HCC) patients. This study aimed to estimate safe cut-off levels of preoperative factors to avoid PHLF after right hepatectomy for HCC.

Methods: A retrospective analysis of the medical records of 90 patients who underwent right hepatectomy for hepatocellular carcinoma from March 2008 to December 2013 was performed. We evaluated the PHLF prevalence and defined that the clinical relevant PHLF (CR-PHLF) is more than grade B according to the suggestion by International Study Group of Liver Surgery (ISGLS). The relationship between the CR-PHLF and preoperative risk factors, such as platelet counts, bilirubin level, ICG R15, liver stiffness by Fibroscan®, the ratio of the future remnant liver volume to the total functional liver volume (RLV/TFLV) and the ratio of the future remnant liver volume to body weight (RLV/Bwt) were investigated.

Results: Among 90 patients, there were 15 patients (16.7%) with CR-PHLF, 75 patients (83.3%) without CR-PHLF (No CR-PHLF group) after right hepatectomy for HCC. In the CR-PHLF group, platelet

counts was lower (121.0 vs. 168.5 × 109/L, p=0.000), total bilirubin was higher (0.8 vs. 0.7 mg/dL, p=0.030), liver stiffness score was higher (12.1 vs. 9.9 kPa, p=0.025), RLV/TFLV was smaller (31.8 vs. 38.9%, p=0.001) and RLV/Bwt was smaller (0.51 vs. 0.69%, p=0.002) than in the No CR-PHLF group. By the multivariable analysis, platelet counts ≤ 138 × 109/L (Exp(B)=14.812, 95% CI: 2.771-79.181, p=0.002) and RLV/TFLV ≤ 34.79% (Exp(B)=9.302, 95% CI: 1.644-52.652, p=0.012) were independent predictive factors for CR-PHLF.

Conclusion: Platelet counts and RLV/TFLV are powerful parameters to predict CR-PHLF after right hepatectomy for HCC.

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The Validity of Two-dimensional Shear Wave Ultrasound (GE Elastography) for Assessing Fibrosis Stage in Patients with Chronic Liver Disease

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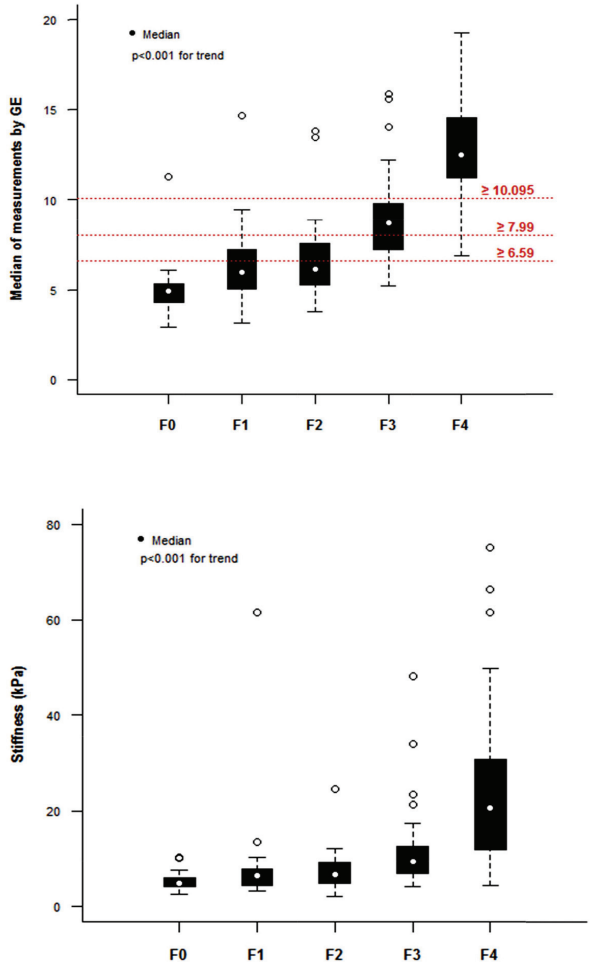

Figure. Distribution of 2D-SWE and fibroscan values according to the fibrosis stage

Table. Distribution of GE Elastography measurement and stiffness according to the fibrosis stage

F1	F2	F3	F4	P for trend*
6.42 ± 2.34	6.48 ± 2	8.97 ± 2.74	12.69 ± 2.88	<0.001
9.08 ± 12.26	7.16 ± 3.46	12.06 ± 9.26	24.89 ± 16.83	<0.001

* P-value was calculated by Jonckheere-Terpstra test for rend.

Aims: Several real-time two-dimensional shear wave elastography (2D-SWE) have been developed to assess liver fibrosis with readily use of combining elastography and traditional ultrasound imaging. However, compared with transient elastography (fibroscan), the diagnostic accuracy and clinical usefulness of these methods were not fully validated. In this study, newly developed 2D-SWE (LOGIQ E9, GE healthcare, UK) was evaluated for predicting liver fibrosis stage and compared with fibroscan.

Methods: Out of 1,395 patients who received 2D-SWE during May 2015 to Apr 2016, seventy (5.0%) who failed to get available value of 2D-SWE due to obesity and 131 (9.4%) with high value of AST or ALT were excluded in the analysis. Liver biopsy was performed in 177 patients. 2D-SWE measurement was considered valid 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).

Results: Patients were male predominant (60.8%), their mean age was 50.4±12.4 years old and most common etiology of liver disease was hepatitis B (40.3%) followed by alcohol (26.1%). Liver fibrosis stage consisted of F0 (14.1%), F1 (12.4%), F2 (28.8%), F3 (18.1%) and F4 (26.6%). Overall, 2D-SWE was well correlated with transient elastography (r=0.788, P<0.001). 2D-SWE median values (kPa) increased with increasing stage of liver fibrosis [F0 (5.0±1.5), F1 (6.4±2.3), F2 (6.5±2.0), F3 (9.0±2.7), F4 (12.7±2.9)] (p for trend <0.001). For the diagnosis of liver cirrhosis, AUROCs and optimal cutoff of 2D-SWE were 0.928 (95% confidence interval [CI], 0.890-0.967) and 10.1 kPa. The sensitivity, specificity, positive predictive value and negative predictive value for predicting cirrhosis were 82.2%, 92.2%, 78.7% and 93.7% respectively. For diagnosing significant liver fibrosis (≥F2), AUROCs and optimal cutoff of 2D-SWE were 0.913 (95% CI, 0.870-0.956) and 7.99 kPa.

Conclusions: With effective comparability to fibroscan and availability of a conventional ultrasound examination, 2D-SWE is an useful tool for stratifying liver fibrosis stage and diagnosing liver cirrhosis.

Keywords: Liver fibrosis, Transient elastography, 2D-SWE

13. HCC, Clinical

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Characteristics of First Diagnosed Hepatocellular Carcinoma in Liver Cirrhotic Patients during 15 Years : Multicenter Retrospective Study in Daegu-Gyeongbuk Province

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Aims: We aimed to evaluate the characteristics of first diagnosed as hepatocellular carcinoma(HCC) in liver cirrhotic patients in Daegu-Gyeongbuk province in Korea during recent 15 years.

Methods: We reviewed retrospectively medical records of 15,716 liver cirrhotic patients of 5 university hospitals with KCD-6 codes in Daegu-Gyeongbuk province from 2000 to 2014.

Results: 1. Among 15,716 cirrhotic patients, 1,339 patients(8.5%) diagnosed as HCC. Mean age was 61.2±10.9 years old, men were 975(72.8%) and women were 364(27.2%). The mean time to diagnose as HCC after initial diagnose as cirrhosis was 3.91±2.79 years.

2. Mean annual incidence of HCC was 2.79%. At time of diagnosis, Child-Turcotte-Pugh(CTP) class A was 45.3%, B was 44.8% and C was 9.96%. Mean CTP score was 7.02±1.82. Underlying liver disease were HBV(61.5%), alcohol(19.2%), HCV(9.0%), NAFLD(1.9%) and others.

3. Mean time to diagnose as HCC were 4.01±2.85 years for HBV, 3.48±2.59 years for HCV, 3.96±2.87 years for alcohol, 3.00±1.91 years for NAFLD after initial diagnose as cirrhosis. Mean time to diagnose HCC were 4.98±3.29, 3.47±2.13, 2.28±1.28 years when accessed by five-year intervals (p<0.001), mean CTP score were 7.25±1.87, 6.98±1.80, 6.64±1.67 (p=0.003)

4. There were not significant clinical and laboratory differences in patients diagnosed as HCC within 5 years and beyond 10 years after initial diagnosed as cirrhosis.

Conclusions: The time intervals between initial diagnosis as cirrhosis and HCC are significantly reduced. It may caused by active cancer surveillance and advanced diagnostic modalities. Among the various causes of liver cirrhosis, NAFLD has the shortest time interval to diagnoses HCC. So, we need to carefully monitor cirrhotic patients caused by NAFLD.

Keywords: Liver cirrhosis, Hepatocellular carcinoma

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Risk Assessment of Developing Hepatocellular Carcinoma Using Wisteria Floribunda Agglutinin-positive Human Mac-2 Binding Protein in Chronic Hepatitis B Patients

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Aims: Wisteria floribunda agglutinin-positive human Mac-2 binding protein (WFA+-M2BP) is a serologic marker corresponding with degree of liver fibrosis. However, to date, few studies have investigated its prognostic role. Thus, we evaluated whether serum WFA+-M2BP can predict the risk of developing hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB).

Methods: A total of 1,323 patients with CHB and avaiable WFA+-M2BP test between 2009 and 2011 were recruited for this retrospective analysis. All patients were followed up to monitor HCC development.

Results: The mean age of the study population (793 men and 530 women) was 51.0 years. On-going antiviral therapy was noted in 352 (26.6%) patients. During the follow-up period (median 60.3 months), 52 (3.9%) patients experienced HCC development. In patients with HCC, age, platelet count, and the proportion of male gender, diabetes, and ultrasonographic cirrhosis were significantly higher than those of patients without HCC (all p<0.05). On multivariate analysis, along with male gender, diabetes, and ultrasonographic cirrhosis (all p<0.05), WFA+-M2BP was as independent predictor of HCC development (adjusted hazard ratio [HR] 1.143, 95% confidence interval [CI] 1.139-1.829; p=0.002). However, antiviral therapy did not influence the risk of HCC development (p>0.05). When a three-tier stratification was applied to our study population using cut-off value of 0.46 and 0.83 to calculated the relative risk of HCC development (n=441 in high group; n=436 in intermediate group; n=446 in low group), patients with high (adjusted HR 5.265, 95% CI 1.160-23.884, p=0.031) and intermediate (adjusted HR 1.561, 95% CI 0.309-7.871, p=0.590) WFA+-M2BP range were found more likely to develop HCC, compared to patients with low WFA+-M2BP range. Cumulative incidence rates of HCC at 5-years were also significantly highest in patients with high WFA+-M2BP range, middle in those with intermediate WFA+-M2BP range, and lowest in those with low WFA+-M2BP range (0.9%, 1.8%, and 6.1%, respectively; high vs. intermediate p<0.001, log-rank test; intermediate vs. low p=0.101 by log-rank test).

Conclusions: WFA+-M2BP determination independently predicted the risk of developing HCC in patients with CHB. Further studies to compare WFA+-M2BP with other surrogates marker for liver fibrosis such as transient elastography are required.

Keywords: Mac-2 binding protein, Hepatocellular carcinoma, Hepatitis B

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The Surveillance Rate and Its Impact on Early Diagnosis and Survival of Hepatocellular Carcinoma in South Korea

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Aims: The regular surveillance for early diagnosis of hepatocellular carcinoma (HCC) is widely recommended for high risk patient, however, its performance is suboptimal in real-life setting. This study aimed to elucidate the rate of performing surveillance and its impacts on early diagnosis and survival in newly diagnosed HCC patients in South Korea.

Methods: In this prospective cohort study, newly diagnosed 350 HCC patients were consecutively enrolled from Mar 2012 to Apr 2016. A structured questionnaire survey on the HCC surveillance status was conducted by attending physicians from each patient with informed consents. Adequate surveillance was defined as serum AFP and liver imaging tests with 6-12 months interval over >2 years.

Results: The adequate surveillance was performed in 92 patients (26.3%, Group 1: semiannual 83.7%, annual 16.3%), while not in 258 patients (73.7%, Group 2). Age and male proportion were not different from the two groups, however, advanced cirrhosis (Child-Pugh class B/C) was more frequent in Group 2 (18.6%) than in Group 1 (8.7%, p=0.026). Group 1 showed higher proportion of early HCC (BCLC stage 0/A, 75%) than Group 2 (50.4%, p-value <0.001).

Group 1 showed longer overall survival (43.4 Mo., 95% CI 40.8-45.9) compared to Group 2 (39.1 Mo., 95% CI 36.7-41.5, p=0.017). The multivariable Cox regression analysis showed that, advanced cirrhosis (HR 1.161, 95% CI 1.79-6.38), and early stage (HR 1.431, 95% CI 3.98-20.67) were independent predictors of overall survival, while regular surveillance was insignificant (HR 1.736, 95% CI 0.82-4.64).

Conclusions: Adequate surveillance was performed in less than one third of newly diagnosed Korean HCC patients, in them, 75% of HCC detected at early stage, which may improve survival of those patients. Comprehensive efforts to optimize the surveillance program for the target population should be urgently established.

Keywords: Hepatocellular carcinoma, Surveillance, Survival

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Comparison of the Incidence of Hepatocellular Carcinoma in HBV, HCV and Non-infection Groups: Population Based Cohort Study

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Aims: The most important risk factor of hepatocellular carcinoma (HCC) in Korea is viral hepatitis. However, there is not enough data comparing the risks between HBV/HCV infection and non-infection group on HCC development.

Methods: The incidence rates of HCC by types of viral hepatitis were compared using 1 million National Sample Cohort of National Health Insurance Service from 2002-2013. For viral hepatitis group, subjects who were diagnosed with HBV/HCV between 2004-2005 without any prior history of the virus infection and HCC during 2002-2003 were selected. For non-infection group, subjects who were free of the virus infection from 2002-2013 without any prior history of HCC during 2002-2003 were selected. The hazard ratio (HR) of HCC development was calculated by Cox proportional hazard (PH) model adjusting for sex and age at infection.

Results: The incidence of HCC development from 2004-2013 was 4.2% (374/88,960) in HBV, 4.1% (87/2,147) in HCV, and 0.3% (1648/536,101) in non-infection group. The incidence density of HCC was 4.99/1,000 person-years in HBV, 5.16/1,000 person-years in HCV and 0.32/1,000 person-years in non-infection groups. The HR of HCC was high in HBV (15.1), HCV (15.5), males (2.2) and old age (1.9, 5.2, 8.8, 13.6, and 17.0 for the 30s, 40s, 50s, 60s, and 70s, respectively). When stratified by age and sex, the risks of HCC development between HBV and HCV group were different. For males, a significantly increased risk was observed in age <60 for HBV group but in age ≥60 for HCV group. For females, which was observed in age <40 in HBV group but in age ≥40 for HCV group.

Conclusions: Adjusted HR was 13.95 in HBV and 11.58 in HCV compared to non-infection group. Since HBV infection is decreasing, the incidence of HCC is expected to increase by HCV infection in old age group.

Keywords: Cohort, HBV, HCV, Hepatocellular carcinoma

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Maintained Virological Remission Should Be the Endpoint during Entecavir Monotherapy

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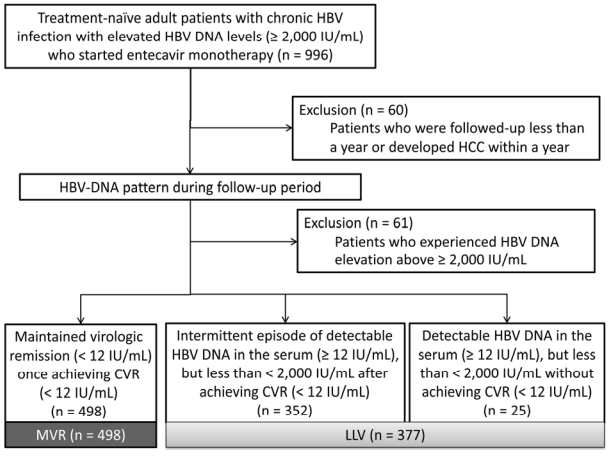
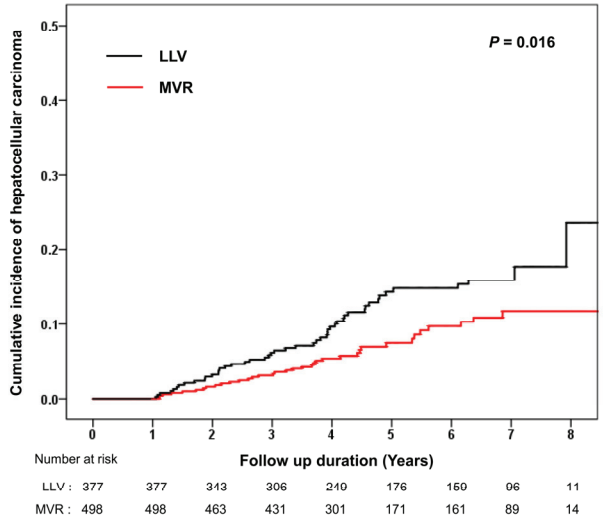
Background and Aims: It is controversial as to whether a change of therapy is needed for patients showing low-level viremia (<2,000 IU/mL) (LLV) on entecavir or tenofovir monotherapy, as long-term health outcome of LLV is not well known.

Methods: A retrospective cohort of 875 treatment-naïve chronic hepatitis B virus (HBV) mono-infected patients [mean age: 47.7 years, male = 564 (64.5%), cirrhosis = 443 (50.6%)] on entecavir monotherapy was analyzed for the development of HCC. HCC risk was compared between patients who showed maintained virological response (MVR), defined by persistently undetectable HBV DNA (< 12 IU/mL), and patients with LLV, defined by either persistent or intermittent episode of detectable HBV DNA but less than 2,000 IU/mL.

Results: During a median 4.5 years of follow-up (range: 1.0 – 8.7 years), HCC was diagnosed in 85 patients (9.7%). The development of HCC was more frequent in patients with LLV than MVR (14.3%

vs. 7.5% at 5-years, p = 0.015). LLV was an independent risk factor associated with HCC development [hazard ratio (HR), 95% confidence interval (CI) = 1.98 (1.28-3.06), p = 0.002, adjusted for age, sex, hepatitis B e antigen (HBeAg), baseline HBV DNA levels and cirrhosis]. LLV was more frequently observed in patients without cirrhosis, high viral load and HBeAg positive patients. When stratified, LLV showed higher risk for HCC than MVR for patients with cirrhosis, intermediate viral load, and HBeAg negative patients. **Conclusion:** LLV was associated with increased risk of HCC than MVR among patients on entecavir monotherapy. MVR should be the endpoint of therapy during entecavir monotherapy.





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A Novel Biomarker-based Model for the Prediction of Response to Sorafenib and Overall Survival for Advanced Hepatocellular Carcinoma: A Prospective Cohort Study

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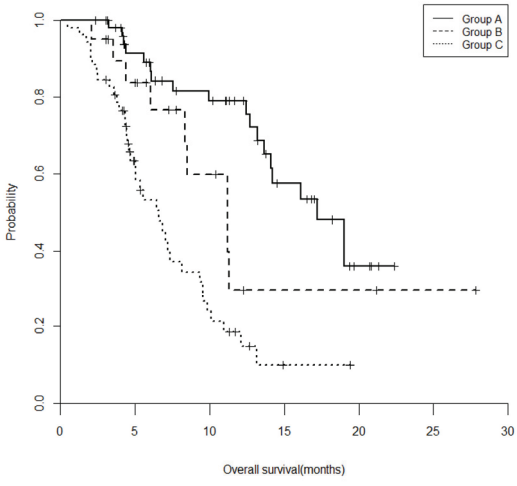
Aims: Sorafenib is the standard therapy for patients with advanced hepatocellular carcinoma (HCC). However, validated biomarkers for prediction of outcome with sorafenib therapy are lacking. The aims were to develop and validate a biomarker-based model for predicting sorafenib response and overall survival (OS).

Methods: This prospective cohort study included 124 consecutive patients (44 achieving disease control and 80 experiencing progression) with Child-Pugh class A liver function who received sorafenib for advanced HCC. Potential serum biomarkers (i.e, hepatocyte growth factor [HGF], fibroblast growth factor [FGF], vascular endothelial growth factor receptor-1, CD117, and angiopoietin-2) were tested. After identification of independent predictors of the tumor response, a risk scoring system for predicting OS was developed and 3-fold internal validation was conducted.

Results: A risk scoring system was developed using six covariates: etiology of underlying liver disease, fibrosis index score, and serum levels of PIVKA-II, HGF, and FGF (Table 1). When we stratified patients into group A (risk score <9), B (9≤risk score<10), and C (risk score ≥10), this model provided good discriminant functions on tumor response (c-index=0.869) and 12-month survival (AUC=0.825). Median OS times were 17.2 mo in group A, 11.2 mo in group B, and 6.6 mo in group C, respectively (P<0.001, Figure 1). In internal validation, the model maintained good discriminant functions on tumor response (c-index=0.855), 12-month survival (AUC=0.828)

Table 1. Scoring system for the prediction of sorafenib response and overall survival.

Variable	Score=0	Score=1	Score=2
Etiology of underlying liver disease	Non-HBV/HCV	HCV	HBV
BCLC stage	0/A	B	C/D
Fibrosis index	<2	2-5	>5
PIVKA-II (mAU/mL)	<30	30-1780	>1780
FGF (pg/mL)	<2	2-5	>5.5
HGF (pg/mL)	<1380	1380-1860	>1860



No. at Risk	0	5	10	15	20	25	30
Group A	52	40	30	14	4	0	0
Group B	20	15	7	2	2	1	0
Group C	52	25	9	1	0	0	0

and good calibration functions (all P>0.05 between expected and observed values).

Conclusions: This new model including serum FGF and HGF showed good performance in the prediction of response to sorafenib as well as survival in patients with advanced HCC. Value of those serum markers in risk stratification and decision of therapeutic agents needs further studies.

Keywords: Hepatocellular carcinoma, Sorafenib, Response, Prediction

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Low Levels of Circulating MicroRNA-26a/29a as Poor Prognostic Markers in Patients with Hepatocellular Carcinoma Who Underwent Curative Treatment

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Aim: We aimed to evaluate prognostic implication of circulating microRNA (miR)-21, 26a, and 29a in patients with hepatocellular carcinoma (HCC) who underwent hepatic resection or radiofrequency ablation (RFA) for curative treatment.

Methods: A total of 120 patients with hepatitis B virus (HBV)-related HCC who underwent surgical resection (n=63) or RFA (n=57) were included. Expression levels of miR-21, 26a, and 29a in pretreatment plasma were assessed by fold change of Ct values acquired by quantitative real-time polymerase chain reaction. Several clinical variables and pretreatment circulating miRs were analyzed for identifying prognostic markers by using Kaplan-Meier analysis and Cox regression analysis.

Results: Univariate analysis showed that age, low albumin level, low platelet count and advanced tumor stage (modified UICC stage III, IV), low miR-26a (Hazard ratio [HR]=1.72; 95% confidence interval [CI]=1.04-2.83; P=0.035) and low miR-29a (HR=1.75; 95% CI=1.04-2.94; P=0.035) were identified as independent risk factors of poor disease-free survival (DFS).

In the analysis of liver transplantation (LT)-free survival, all of low miR-21, miR-26a and miR-29a were associated with poor LT-free survival in univariate analysis. However, multivariate Cox regression analysis revealed that low miR-26a (HR=3.41; 95% CI=1.32-8.82; *P*=0.011) and low miR-29a (HR=2.75; 95% CI=1.10-6.85; *P*=0.030), low platelet count and advanced tumor stage were significantly associated with poor LT-free survival. Circulating miR-21 was not significantly associated with both DFS and LT-free survival in multivariate analysis, even though miR-21 was positively correlated with tumor size and tumor stage. Correlation analysis showed remarkable correlation between circulating miR-26a and miR-29a (Spearman's rho = 0.734, P<0.001).

Conclusion: Pretreatment levels of circulating miR-26a and miR-29a were independent prognostic markers for predicting poor DFS and LT-free survival in patients with HBV-related HCC who underwent hepatic resection or RFA.

Keywords: Hepatocellular carcinoma, MicroRNA-21, MicroRNA-26a, MicroRNA-29a, Prognostic marker, Disease free survival

14. HCC, Clinical

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Transplantation versus Hepatectomy for Hepatocellular Carcinoma Less than 2 cm: The Experience of Ajou University Hospital

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Aims: Surgical resection has been the treatment of choice for hepatocellular carcinoma (HCC), and the overall survival was satisfied. However, the recurrence is a significant problem. The shortage of organ donors has led to a restricted indication for orthotropic liver transplantation for HCC. The aim of this study was to analyze the results of surgical treatment for HCC (≤2cm).

Methods: From January 2005 to December 2013, 619 consecutive HCC patients underwent surgical treatment at our institution. 119 (20.8%) HCC patients who the diameter of tumor was less than 2 cm were retrospective. We excluded one case of incidental HCC and 4 cases hospital motality patients who were received liver transplantation. Finally, 114 HCC patients were enrolled in this study and they were divided into two groups by treatment procedure. One group is hepatectomy group (n=79), the other is transplantation group (n=35).

Results: The median follow-up period was 40.5 months. Totally, 30 cases were experience tumor recurrence in the follow-up period, 29 of them were come from hepatectomy group, while only one case was from transplantation group. Figure 1 shows us the Treatment modalities for recurrent cases after initial hepatectomy. The 1, 3 and 5-year recurrence free survival rates of hepatectomy group were 85.8%, 68.3% and 50.9%, and those of transplantation group were 97.1%, 97.1% and 97.1%, respectively. (P=0.000) The 1, 3, and 5-year survival rates of hepatectomy group were 97.5%, 93.4% and 90.8%, and those of transplantation group were 100%, 96.9%, and 96.9%, respectively. (p=0.819)

The cutoff value (38.5u/L) of serum ALT was detected by ROC cure (Area under the cure=0.709, P value=0.002) . We divided the hepatectomy group into two sub group: normal and elevated ALT group according the cutoff value. Elevated ALT group have worse disease free survival (P=0.005) and overall survival (p=0.225)(Firgure3). Figure 4 shows us that the overall survival of normal ALT group have a comparable overall survival to transplantation group, whereas the overall survival of elevated ALT group was worse than transplantation group (P=0.034).

Conclusions: Our results show that transplantation could be a radical treatment for HCC ≤2cm in oncology. However, nowadays, transplantation is still mainly used for HCC patients combined with end stage liver diseases due to the shortage of organ donors. In the subgroup which elevated ALT group, patients have high incidence of recurrence and lower overall survival time. Transplantation as the first line of treatment modalities may be benefit for the patients with elevated ALT.

Keywords: Hepatocellular carcinoma, Transplantation, Hepatectomy

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Comparison of Treatment Outcome between Living Donor Liver Transplantation and Sorafenib for Hepatocellular Carcinoma Patients beyond the Milan Criteria

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Aims: For unresectable hepatocellular carcinoma (HCC) patient, sorafenib is the only systemic treatment showing a survival gain, which, however, is only several months. We have recently reported that patients with low MoRAL score (= 11 X √PIVKA-II + 2 X √AFP) had excellent treatment outcome with 5-year survival rate exceeding 80% after living donor liver transplantation (LDLT) even though they had HCC beyond the Milan criteria (MC) only if there was no extrahepatic metastasis. In the present study, we investigated whether LDLT offers better treatment outcome than sorafenib for HCC patients beyond the MC.

Methods: A total of 325 consecutive patients (122 patients in LDLT group; 203 patients in sorafenib group) beyond the MC who were treated with either LDLT or sorafenib between June 2005 to December 2014 at a single tertiary hospital were included. Patients with extrahepatic metastasis were excluded. The primary and secondary endpoints were overall survival (OS) and time-to-progression (TTP), respectively. Baseline characteristics were balanced using inverse probability weighting (IPW).

Results: Baseline age, Child-Pugh score, and AJCC 7th T classification were significantly different between the two groups, all of which favored the sorafenib group. When the baseline characteristics were balanced using IPW, the sorafenib group experienced significantly higher risk of tumor progression (hazard ratio [HR], 7.3; 95% confidence interval [CI], 4.2–12.8; P<0.0001) and death (HR 10.2; 95% CI, 4.9–21.1; P<0.0001) compared to the LDLT group. Median OS was 34.8 months in the LDLT group and 8.2 months in the sorafenib group (P<0.0001). Increase in OS from LDLT over sorafenib was more predominant among those patients with low MoRAL score (≤314.8) (HR, 16.0; 95% CI, 5.8–44.5; P<0.0001), compared to those with high MoRAL score (>314.8) (HR, 2.4; 95% CI, 1.0–5.6; P=0.047). Among patients with low MoRAL, 5-year tumor progression rate of LDLT group was only 24.1%, while that of sorafenib group was as high as 100%.

Conclusions: For HCC patients beyond the MC, LDLT exhibited significantly longer TTP and OS compared to sorafenib. Therefore, beyond the MC patient with a low MoRAL score and without extrahepatic metastasis might be a good candidate for LDLT rather than sorafenib treatment, if there is a willing living-related donor.

Keywords: Hepatocellular carcinoma, MoRAL score, Living donor liver transplantation, Sorafenib

O - 118

The Comparison of Percutaneous Radiofrequency Ablation with Laparoscopic Radiofrequency Ablation on Overall Survival and Recurrence of Hepatocellular Carcinoma

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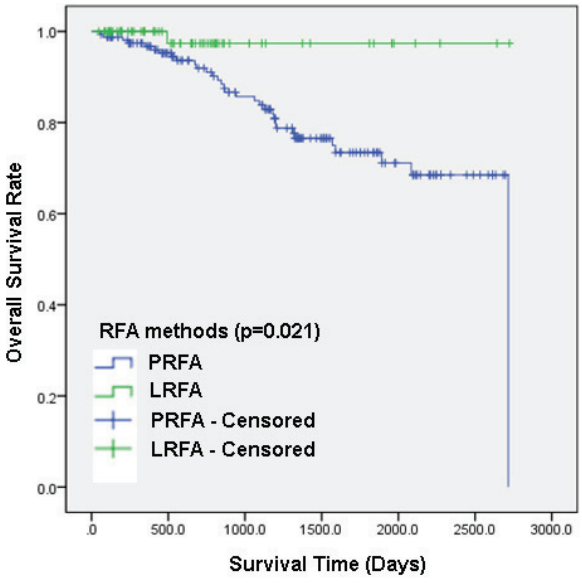
Aims: Laparoscopic radiofrequency ablation (LRFA) allows treatment of hepatocellular carcinoma (HCC) in difficult locations and more accuracy under real time imaging guidance compared with percutaneous RFA (PRFA). However, there are little studies comparing the efficacy and survival outcome of LRFA to PRFA. This study aims to evaluate the comparative effectiveness of the two RFA modalities on the treatment outcomes for HCC.

Methods: From December 2008 to February 2015, clinical outcomes of 226 HCC patients PRFA (n=160) or LRFA (n=66) were analyzed and compared for baseline characteristics, overall survival, and disease-free survival, retrospectively.

Results: There was no significant difference of patient characteristics between two groups that received PRFA or LRFA, except minor differences of background liver disease and several tumor characteristics. Especially, the portion of hepatic cirrhosis patients was higher on LRFA (84.3%) compared with PRFA (73.8%) (p=0.023) and number



of tumor nodule per patient and TNM stage of HCC was statistically higher on LRFA compared with PRFA (p<0.001, and p<0.001, respectively). On univariate analysis, previous transarterial chemoembolization (TACE) experience before RFA for HCC have statistical significance on disease-free survival of both two groups (p<0.001). However, TACE experience before RFA between two groups were not shown significant difference (p=0.194) on baseline analysis. In addition, there was no significant difference between PRFA (1379.9 days, 95% C.I. 1194.0~1565.7) and LRFA (1244.6 days, 95% C.I. 984.6~1504.5) on Kaplan-Meier Estimates of disease-free survival for HCC (p=0.580). However, there was significant difference between PRFA (2203.0 days, 95% C.I. 2044.6~2361.4) and LRFA (2665.3 days, 95% C.I. 2551.7~2778.8) on Kaplan-Meier Estimates for overall survival on HCC (p=0.021). In other words, the patients received LRFA were shown higher overall survival compared with PRFA on log-rank test.

Conclusions: In HCC treatment, the patients received laparoscopic RFA have higher overall survival compared with percutaneous RFA irrespective of previous therapeutic modality.

Keywords: Hepatocellular carcinoma, Percutaneous radiofrequency ablation, Laparoscopic radiofrequency ablation, Overall survival

O - 119

A Multimarker Panel Predicts Complete Response after Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

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Aims: Achievement of a complete response (CR) after transarterial chemoembolization (TACE) is the most robust predictor of favorable outcomes in patients with hepatocellular carcinoma (HCC). The aim of this study was to identify blood-based biomarkers to predict a sustained CR after TACE using targeted proteomics.

Methods: Consecutive patients with HCC who had undergone TACE were drawn from our prospective cohort [training set (n=100) and validation set (n=80)]. Serum samples were obtained before and 6 months after TACE. Treatment responses were evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Multiple reaction monitoring-mass spectrometry (MRM-MS) was used to measure marker candidate proteins (MCPs) with regard to their association with the recurrence of HCC and a sustained CR after TACE.

Results: In the training set, the MRM-MS assay identified 5 MCPs (MRM-MS marker panel). When this 5-marker panel was combined with the best-performing clinical variables (tumor number, baseline PIVKA, and baseline AFP), the resulting ensemble model had the highest area under the receiver operating curve (AUROC) value in predicting a sustained CR after TACE in the training and validation sets (0.881 and 0.813, respectively). Further, the ensemble model remained an independent predictor of rapid progression (hazard ratio, 2.889; 95% confidence interval, 1.612-5.178; P<0.001) in the entire population by multivariate analysis.

Conclusions: Our ensemble model before TACE can predict a sustained CR after TACE. Therefore, this model can aid in determining the best candidates for TACE and the need for adjuvant therapy.

Keywords: Hepatocellular carcinoma, Multiple reaction Monitoring-mass spectrometry, Transarterial chemoembolization, Complete response

O - 120

Outcomes of Stereotactic Ablative Radiotherapy Combined with Transarterial Chemoembolization in Hepatocellular Carcinoma

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Aims: We investigated the local control rate and predictive factors associated with survival of stereotactic ablative radiotherapy (SABR) for hepatocellular carcinoma (HCC) patients treated in combination with transarterial chemoembolization (TACE).

Methods: We retrospectively investigated 75 patients treated with SABR for hepatic tumors from August 2008 to April 2016. Of the 46 consecutive tumors diagnosed as HCC, 30 hepatic tumors from 28 patients were treated with TACE and two hepatic tumors had additional radiofrequency ablation (RFA) before SABR. We evaluated local control rate after SABR and predictive factors associated with overall survival.

Results: The median dose of SABR was 57 Gy (range, 20-60 Gy) in 2-5 fractions. The median follow up duration after SABR for all patients was 50.7 months (range, 6-144.3 months). Twenty two HCCs (73.3%) treated by TACE achieved local complete response (LCR) after subsequent treatment by SABR. The remaining eight tumors (26.7%) showed incomplete response and were further treated with other modalities. The median overall survival (OS) from SABR of all patients was 93 months (95% C.I. 62.942-122.992). And 1-, 3-, 5- year OS rates of all patients were 88.1%, 74.4%, and 66.2%, respectively. The median OS was 93months for LCR group and 17.5 months for incomplete response group with significant difference between two groups (*p=0.003*). Univariate analysis identified tumor size and Child-Turcotte-Pugh (CTP) score as significant predictive factors for OS (*p=0.056; p=0.051*). In multivariate analysis, CTP score was significantly associated with better OS (HR=0.2, *p=0.051*).

Conclusions: SABR can be an effective local therapeutic tool for HCC patients treated with TACE. Especially, CTP score was predictive factor for

better OS when SABR was combined with TACE.

Keywords: Hepatocellular carcinoma, Stereotactic ablative radiotherapy, Transarterial chemoembolization

O - 121

The Efficacy of Radiotherapy-based Multidisciplinary Treatment in Patients with Hepatocellular Carcinoma

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Aims: Recently, radiotherapy is widely used, alone or in combination with various therapeutic modalities, for treating patients with hepatocellular carcinoma (HCC) in Korea. In this study, we investigated the efficacy of radiotherapy-based multidisciplinary treatment in patients with HCC.

Methods: We investigated 216 patients with HCC who underwent radiotherapy to the liver and/or intra-abdominal organs including lymph nodes in Korea University Anam hospital from 2005 to 2015. Radiotherapy was used in combination with transarterial chemo-embolization (TACE), hepatic arterial chemo-infusion or radiofrequency ablation in order to overcome insufficient treatment response or treatment failure. Tumor staging was based on Barcelona Clinic Liver Cancer (BCLC) system. Treatment response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) assessment. Overall survival was calculated using Kaplan-Meier analysis.

Results: The mean age of patients was 59.1 ± 10.4 years and proportion of male gender was 81.9%. Median (range) duration of follow-up was 8.4 (0.4-113.7) months. Among the patients, 8 belonged to BCLC stage A, 12 to BCLC B, and 182 to BCLC C. The best overall treatment response (CR/PR/SD/PD) was 62.5%/12.5%/12.5%/12.5% in BCLC stage A, 8.3%/33.3%/16.7%/41.7% in BCLC B, 1.6%/24.2%/30.2%/44.0% in BCLC C patients. Eight patients with intermediate or advanced stage HCC were bridged to curative resection (n=4) or liver transplantation (n=4) after down-staging had been achieved by the radiation-based multidisciplinary treatment. Cumulative overall survival rates (1 year/3 year/5 year) in Child-Pugh grade A patients were 100%/100%/0% for BCLC stage A (n=3), 60.6%/13.5%/13.5% for BCLC B (n=11), 46.6%/7.9%/5.4% for BCLC C (n=128) and those in Child-Pugh grade B patients were 0%/0%/0% for BCLC stage A (n=5), 100%/100%/100% for BCLC B (n=1), 24.3%/7.4%/0% for BCLC C (n=64).

Conclusions: Radiotherapy can be one of effective treatment in patients with early, intermediate, and advanced HCC.

Keywords: Hepatocellular carcinoma, Radiotherapy

O - 122

Laparoscopic Liver Resection of Hepatocellular Carcinoma with a Tumor Size Larger than 5 cm: Review of 45 Cases in a Tertiary Institution

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Aims: Although laparoscopic liver resection has developed rapidly, its usefulness for the treatment of large tumors is less clear, due to concerns about compromising oncological principles and patient safety. The purpose of this study was to explore the feasibility and safety of laparoscopic liver resection for the treatment of hepatocellular carcinoma (HCC) with a tumor size larger than 5 cm.

Methods: From January 2007 to December 2014, we performed laparoscopic liver resection in 45 patients with HCC with a tumor size ≥ 5 cm. Perioperative outcome, tumor recurrence and overall patient survival were analyzed.

Results: Median age was 60 years old (IQR 52-68) and 64.4% (29/45) was male. Seven patients (15.6%) had larger than 10cm of HCC. No operative deaths occurred and six of the laparoscopic procedures were converted to open resection (conversion rate 13.3%). Median operation time was 365 minutes (IQR 277-443) and median estimated blood loss (EBL) was 400.0 ml (IQR 275-600). There was no R1 or R2 resection and median resection margin was 19.0 mm (IQR 8.0-33.0). Complications above Clavien-Dindo classification grade III occurred in four patients (8.9%). The median overall follow-up time was 10.7 month (range 1.1-62.1). 1-year recurrence free survival (RFS) and overall survival (OS) were 86.0% and 95.5%, and 3-year RFS and OS were 70.7% and 86.0%.

Conclusions: Laparoscopic liver resection seems safe and feasible in patients with HCC with a tumor size larger than 5 cm. Expansion of indication for laparoscopic liver resection in patients with HCC may be considered.

Keywords: Hepatectomy, Hepatocellular carcinoma, Laparoscopy

Poster Oral Presentation

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

[Group 1] June 17, 2016 | 15:30-16:30

Cell Biology and Basic

PO-001

Establishment of Hepatoma Treatment Model Using Hepatoma Cell Spheroids

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Aims: Three dimensional (3D) spheroid cells are more closely mimic natural tissues and organs than cells grown in 2D. 'Biocompatible spheroidal hepatoma cell' is thought to be closest model of real patient's HCC. We have made spheroidal hepatoma cells using the proven technology and already confirmed apoptotic effect of ginsenoside Rh2 and Rg5 on 2D cells (Huh7 and Huh7.5.1). In this study, we investigate apoptotic effects of ginsenoside Rh2 and Rg5 using 3D hepatoma cell spheroids.

Methods: Huh7 and Huh7.5.1 cells were maintained in culture dishes in RPMI supplemented with 10% inactivated fetal bovine serum (FBS) and DMEM supplemented with 10 % dialyzed FBS, respectively. When they reached about 80 % confluence, cells were harvested from 2-D petri-dish cultures by treatment with trypsin. These cells cultured in 1.5 % soft agarose gels for 10-14 days. After 10-14 days, 3-D hepatic structure was formed and treated with ginsenoside Rh2 (100, 200uM) and Rg5 (10, 50, 100uM) for 72h. Comparison between 2-D and 3-D models was done with microscopic and protein analysis.

Results: The behaviors of 2D and 3D cells (Huh7 and Huh7.5.1, respectively) have been shown different morphologic change. 3-D culture of Huh7 and Huh7.5.1 cells had a longer survival time rather than 2-D cell model. The response to ginsenoside Rh2 and Rg5 on 3D culture systems showed a lower cell death rate compared with 2D culture systems. The expression of cleaved PARP protein was increased in both 2D and 3D cells with exposure to ginsenoside Rh2 and Rg5.

Conclusions: Hepatoma cell sheroids had a longer survival time and a similar apoptotic effect compared to 2-D cell model in drug screening. It is expected to have an important role on the drug screening and treatment prediction in HCC.

Keywords: Hepatoma Cell Spheroids, Hepatoma Treatment Model, Ginsenoside Rh2, Ginsenoside Rg5

PO-002

Upregulation of NADPH Oxidase 4 and Oxidative Stress via TGF-β-ERK-mTOR Pathway in Transdifferentiation of Mouse Hepatic Stellate Cells

Soo Jin Kim[1], Kyu Hee Hwang[1], Ji Hee Kim[1], Moon Young Kim[2], Soon Koo Baik[2], Seung Kuy Cha[1], Ranjan Das[1], Kyu Sang Park[1]

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Aims: Liver cirrhosis results from chronic hepatotoxic injuries, characterized by fibrotic changes with accumulation of extracellular matrix. The principal mediator of fibrosis is known as transdifferentiation of hepatic stellate cells (HSCs) into myofibroblasts. Oxidative stress is involved in the initiation of this process, however, molecular mechanism of reactive oxygen species (ROS) generation from HSCs has not been clearly identified.

Methods: Liver fibrosis in mice was developed by thioacetamide (TAA) administration. Mechanistic studies were conducted using primary HSCs isolated and purified from Balb/C mice of 20 weeks of age. RNA and protein levels were quantified by real-time PCR and western blotting, respectively. ROS generation was measured by a confocal imaging system with DCF fluorescence dye.

Results: We observed consistent and marked upregulation of NADPH oxidase 4 (NOX4) along with α-smooth muscle actin (α-SMA) and plasminogen activator inhibitor 1 (PAI-1) in the process of hepatic fibrosis development. Increased expression of TGF-β and activation of its downstream signaling cascades including extracellular signal-regulated kinases (ERK) and mammalian target of rapamycin (mTOR) were prominent at the early period of TAA treatment. In primary mouse HSCs, upregulation of α-SMA, PAI-1 and vimentin were evident during culture. We also observed time-dependent increase in TGF-β and NOX4 protein levels as well as activation of ERK1/2 and mTOR pathways. Consistent with NOX4 upregulation, cytosolic ROS was elevated during myofibrotic changes in primary HSCs, which was attenuated by SB431542 (TGF-β receptor blocker), PD184352 (ERK inhibitor) or rapamycin (mTORC1 inhibitor).

Conclusions: We suggest that oxidative stress during transdifferentiation of HSCs may be originated from increased NOX4 protein triggered by TGF-β-ERK-mTOR axis, inhibition of which could be an effective therapeutic target to prevent the progression of liver cirrhosis.

Keywords: HSC, TGF-β, mTOR, NOX4

PO-003

Regulation of Tumor Angiogenesis and Endothelial Mesenchymal Transition by Dickkopf-1

Sung Hoon Choi[1], Hyun Gyu Lee[3], Hyemi Kim[3], Jun Young Park[1,2], Beomkyung Kim[1,2], Do young Kim[1,2], Sang Hoon Ahn[1,2], Kwang-Hyub Han[1,2], and Seung Up Kim[1,2]

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Aims: Tumor angiogenesis is essential for invasive tumor growth and metastasis.

Dickkopf (DKK)-1, an antagonist of Wnt signal, participates in tumor

development and progression. This study evaluated whether DKK-1 stimulation increases angiogenesis and endothelial mesenchymal transition. (EnMT)

Methods: Human umbilical vein endothelial cells (HUVECs) were stimulated with recombinant DKK-1 or concentrated conditioned medium from human hepatoma cells or DKK-1-transfected 293 cells. Following stimulation, the expression levels of angiogenesis related factors and EnMT related markers were examined by immunoblot assays. In addition, the effect of exogenous DKK-1 on angiogenesis and EnMT were assessed by endothelial cell tube formation assay, cell invasion assay and wound healing assay.

Results: Human hepatoma cells such as Hep3B and Huh-7 showed high expression levels of DKK-1, whereas 293 cells and HUVECs showed little or no expression. Increased endothelial cell tube formation and invasiveness were observed in HUVECs treated with either concentrated conditioned medium from DKK-1-overexpressed 293 cells, human hepatoma cells, or recombinant DKK-1. Increased cell motility was also shown in DKK-1-stimulated HUVECs in wound healing assay. Furthermore, the expression level of angiogenesis-related factors including vascular endothelial growth factor receptor 2 and vascular endothelial-cadherin was increased in DKK-1-stimulated HUVECs. In addition, the expression of EnMT markers such as vimentin and Twist was also increased in DKK-1-stimulated HUVECs.

Conclusions: Our in vitro data suggest that DKK-1 enhances angiogenic and EnMT properties of HUVECs. Modulation of DKK-1 may shed light on development of novel strategies to control tumor angiogenesis and metastasis.

Keywords: Dickkopf-1, Angiogenesis, EnMT

PO - 004

Increased Phosphatase of Regenerating-1 by Placental Stem Cells Promote Hepatic Regeneration in a Rat Model with Bile Duct Ligation

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Aims: Phosphatase of regenerating liver-1 (PRL-1) controls diverse cellular processes including liver regeneration. However, it is still unknown whether MSCs influence PRL-1 expression during regeneration of a damaged liver. We therefore investigated PRL-1 expression and its functions in bile duct ligation (BDL) following transplantation (Tx) with CP-MSCs.

Methods: CP-MSCs and WI-38 cells labeled with fluorescent dye were engrafted into BDL model via intravenous Tx. Expression markers related to engraftment and proliferation in hepatic cells were analyzed by quantitative real time-PCR, Western blot and immunofluorescence. Furthermore, BrdU incorporation and FACS analysis were performed to confirm the CP-MSC effect on the regeneration of injured hepatic cells in in vitro.

Results: CP-MSC Tx decreased the level of cirrhosis in a BDL rat model compared with others. The expression of PRL-1 and Rho family-related genes in the liver tissue of a BDL rat model was increased by CP-MSC Tx. Interestingly, CP-MSC migration was also decreased by PRL-1 siRNA treatment. Furthermore, CP-MSC Tx increased the expression of albumin and PRL-1 in liver tissue compared with others as well as the proliferation of hepatocytes in in vitro. However, proliferation and albumin production in primary hepatocytes were decreased by the PRL-1 siRNA treatment.

Conclusions: Taken together, the increase in PRL-1 expression induced by CP-MSC Tx enhanced liver regeneration in a rat hepatic failure model via the dual function of PRL-1 controlling CP-MSC migration and hepatic proliferation. Therefore, these findings reveal a fundamental mechanism of the therapeutic effects of PRL-1 on hepatic diseases resulting from CP-MSC Tx.

Keywords: Placenta-derived mesenchymal stem cell, Engraftment, Liver regeneration, PRL-1

PO - 005

1-Methyl Tryptophan Increase Cell Death of Hepatic Stellate Cells Arrested by Interferon-gamma

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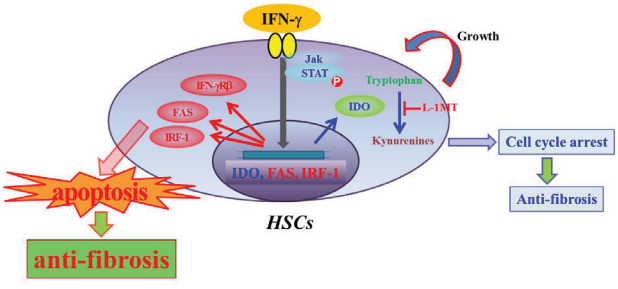
Aims: Liver fibrosis, a precursor to cirrhosis, is the result of deposition of extracellular matrix (ECM) proteins and is mediated primarily by activated hepatic stellate cells (HSCs). In this study, we investigated the effect of interferon (IFN)-gamma on the activation and proliferation of HSCs in vitro.

Methods: Human hTERT immortalized HSCs were kindly given by Dr. KS Lee (Yonsei University, Seoul, Korea). After IFN-gamma treatment, cell signaling pathways and DNA content were analyzed to assess inactivation of HSCs or down-regulation of HSC proliferation. Inhibitor (1-methyl tryptophan; 1-MT) of indoleamine 2,3-dioxygemase (IDO) expressed by IFN-g was used to assess whether IDO played key roles on regulation of activated HSCs.

Results: IFN-gamma significantly inhibited growth of HSCs and down-regulated the expression of alpha-smooth muscle actin (SMA) in HSCs. IDO was dramatically expressed by IFN-gamma through STAT1 activation and resulted in depletion of tryptophan. These depletion induced G1 cell cycle arrest in HSCs. When IFN-gamma-mediated G1



cell cycle arrest was released by treatment with 1-MT, apoptosis was observed dramatically in HSCs through induction of IRF-1 and FAS.
Conclusions: Treatment with IFN-gamma alone or co-treatment with IFN-gamma and 1-MT inhibited growth of HSCs and down-regulated the expression of alpha-SMA in HSCs. Moreover, IFN-gamma and 1-MT induced apoptosis in HSCs through expression of IRF-1 and FAS. Our results suggest that inhibition of IDO enhance the down-regulation of activated HSCs and therefore co-treatment with IFN-gamma and 1-MT can be applied to ameliorate liver fibrosis.
Keywords: Hepatic stellate cell, IFN-gamma, Indoleamine 2,3-dioxygemase, 1-Methyl trypthophan, Cell death

PO - 006

MicroRNA-99a Attenuates HCV Replication through the Downregulation of Subtilisin Kexin Isozyme-1 (SKI-1) / Site-1 Protease (S1P)

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The Catholic University Liver Research Center & WHO Collaborating Center of Viral Hepatitis, The Catholic University of Korea, Seoul, Korea, Department of Internal Medicine, Seoul St.Mary's Hospital, The Catholic University of Korea

Aims: MicroRNAs modulate various biological processes through dysfunction of target genes. Accumulating evidence indicates that a number of miRNAs can regulate or be regulated by hepatitis C virus (HCV) infection. Recently, it has been reported that expression level of miR-99a was inversely correlated with sustained virological response in patients with chronic hepatitis C. However, the exact role of miR-99a and its target in the pathogenesis of HCV infection remains unexplored. Here, we investigated the restrictive effects of miR-99a on the replication of HCV in relation to lipid metabolism and identified subtilisin kexin isozyme-1/site-1 protease (SKI1/S1P) as a novel target of miR-99a.
Methods: The levels of miR-99a were evaluated in the serum of patients with chronic HCV infection, Huh7 cells infected with HCVcc and HCV full-genomic replicon (FGR) cells by miRNA quantitative real-time PCR (qRT-PCR). In addition, the effect of miR-99a-5p on HCV replication was analyzed by measuring the levels of HCV RNA after treatment with miR-99a-5p mimics in Huh7 cells infected with HCVcc and FGR cells. The levels of miR-99a target genes involved in lipid metabolism were also assessed by western blot analysis and qRT-PCR. The change of lipid accumulation by miR-99a-5p over-expression was quantitatively measured by Nile Red staining.
Results: The expression level of miR-99a-5p was significantly down-regulated in sera from patients chronically infected with HCV compared to healthy subjects. Moreover, the expression level of miR-99a was decreased in both of FGR cells and Huh7 cells infected with HCVcc. Notably, treatment with miR-99a-5p mimics significantly down-regulated HCV replication. In this study, we identified SKI1/S1P as a novel target of miR-99a in relation to HCV replication. SKI1/S1P expression was significantly suppressed by treatment with miR-99a-5p mimics in HCV replicating cells. Regarding the role of SKI1/S1P in lipogenesis, the forced expression of miR-99a-5p attenuated the increase in the amount of intracellular lipid droplets after oleic acid treatment.
Conclusions: Our data provide new mechanistic insights of role of miR-99a as an anti-viral host factor on HCV replication by suppression of lipid accumulation through down-regulated of SKI1/S1P.
This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2015R1C1A1A020 37212)
Keywords: HCV, MicroRNA, MiR-99a, Lipid metabolism, Subtilisin kexin isozyme-1 (SKI-1)/ site-1 protease (S1P)

HCV, Clinical

PO - 007

Daclatasvir plus Asunaprevir Therapy in Treatment-naïve and Treatment-experienced Korean Patients with Genotype 1b Chronic HCV Infection: A Single-center, Real-life Experience

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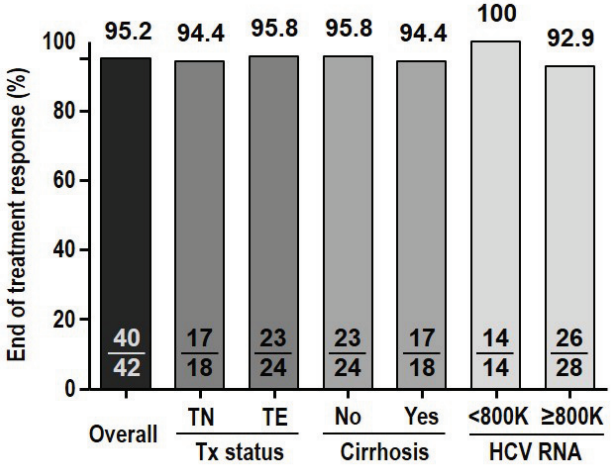
Aims: Daclatasvir in combination with asunaprevir (DCV/ASV) therapy has recently been introduced to Korea for treatment of genotype 1b chronic hepatitis C virus (HCV) infection. To date, the efficacy and safety of DCV/ASV has not been systematically investigated in a real-life clinical setting in Korea. We aimed to assess the efficacy and safety of DCVASV therapy in a real-life cohort of Korean patients with genotype 1b chronic HCV infection.
Methods: Between July 2015 and April 2016, a total of 156 patients with genotype 1b chronic HCV infection were prospectively enrolled and underwent screening for the presence of NS5A resistance-associated variants (RAVs) in Samsung Medical Center, Seoul, Korea. Patients without NS5A RAVs were treated with DCV/ASV for



24 weeks. The primary endpoint was end of treatment response (ETR). Safety evaluations included adverse events.

Results: The incidence of NS5A RAVs was 16.6% (L31M/F/V, 6.4%; Y93H, 10.2%). Overall, 42 patients (treatment-naïve, 18; treatment-experienced, 24) had completed the treatment course. The median age was 65.4 years, and the majority of patients were female (66.6%). Eighteen (42.8%) patients had cirrhosis. ETR was achieved in 40 (95.2%) patients. ETR was comparable between the following subgroup of patients: treatment-naïve (17/18, 94.4%) vs. treatment-experienced (23/24, 95.8%); non-cirrhotic (23/24, 95.8%) vs. cirrhotic (17/18, 94.4%); baseline HCV RNA levels <800,000 IU/ml (14/14, 100%) vs. ≥800,000 IU/mL (26/28, 92.8%). On-treatment virologic response showed undetectable HCV RNA in 38 (95%), 40 (97.5%) and 34 (94.4%) patients at week 4, 8 and 12, respectively. There was 1 serious adverse event leading to treatment discontinuation. The most common adverse events were headache, pruritus and fatigue.

Conclusions: DCV/ASV therapy provided high ETR rates in both treatment-naïve and treatment-experienced genotype 1b chronic HCV-infected patients without NS5A RAVs in Korea. Treatment was generally well-tolerated regardless of cirrhosis status.

Keywords: Daclatasvir, Asunaprevir, Real-life experience, Chronic hepatitis C, Genotype 1b

PO - 008

Early Virologic Response of Korean Chronic Hepatitis C Patients Treated with Daclatasvir and Asunaprevir Combination Therapy

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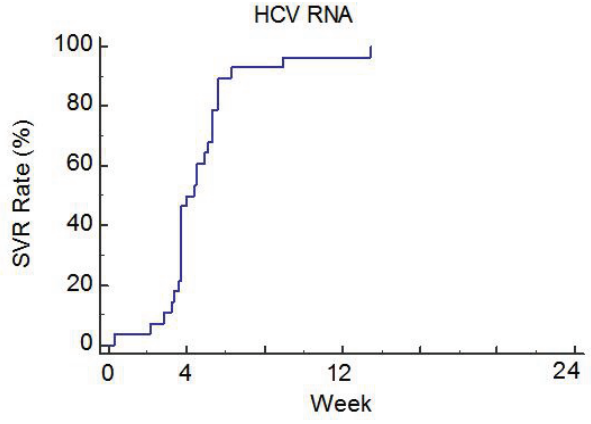
Aims: Direct-acting antivirals have been established as a standard therapy for chronic hepatitis C (CHC) due to their superior efficacy and safety compared to conventional pegylated interferon based regimens. Recently, combination of daclatasvir and asunaprevir (DCV+ASV) has been approved in Korea for the treatment of HCV genotype 1, but real life data were not sufficient yet. This study aimed to explore the early virologic response to DCV+ASV in Korean genotype 1b CHC patients.



Methods: Antiviral-naïve, non-responder with interferon or relapser chronic hepatitis C patients who visited our hospital and started DCV and ASV between October 2015 and March 2016 were identified from the electronic medical record system (BESTCARE).

All patients received daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily for 24 weeks. The primary endpoint was sustained virologic response 24 weeks after treatment. The primary efficacy endpoint was the proportion of patients with HCV RNA <25 IU/mL at 24 weeks after completion of DCV and ASV treatment. SVR rate was assessed by Kaplan-Meier analysis.

Results: Among 28 HCV patients who started DCV and ASV, 15 patients were treatment-naïve CHC, 8 patients were non-responder with interferon treatment, 5 patients were relapse with previous treatment. Baseline characteristics of patients were median age of 35 (range 38-81), high HCV viral loads (median 2,333,185 IU/mL, range 1026 - 10,000,000 IU/mL), and presence of cirrhosis in 55%. All baseline characteristics did not appear to impact response rates. Sixteen patients (60 %) showed undetectable RNA levels (less than 25 IU/mL) within week 4 of treatment, and 12 patients (40%) attained that levels within week 12 of treatment. All of the 28 patients (100%) showed sustained virologic response at the end of 24 weeks of therapy. There was no drop-out cases associated with adverse drug reactions.

Conclusions: 24-week treatment with DCV and ASV provides a highly effective antiviral response in genotype 1B CHC patients.

Keywords: Daclatasvir, Asunaprevir, Chronic hepatitis C

PO - 009

Effect of Baseline Resistance-associated Variants on SVR with the 3D Regimen with and without RBV in GT1a and GT1b-infected Patients

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Aims: The 3 direct-acting antiviral (3-DAA) regimen of ombitasvir, ritonavir-boosted paritaprevir and dasabuvir ± RBV is approved in the US and EU for treatment of hepatitis C virus (HCV) genotype (GT) 1 infection. Baseline resistance associated variants (RAVs) in HCV NS3 or NS5A can impact response to other DAA regimens; we assessed the prevalence and impact of RAVs on response to the 3-DAA regimen.

Methods: Next-generation sequencing (Illumina MiSeq) assessed baseline samples from treatment-naïve (PEARL-IV), -experienced (SAPPHIRE-II), or cirrhotic (TURQUOISE-II) GT1a patients who received 3-DAA + RBV, and treatment-experienced (PEARL-II) or cirrhotic (TURQUOISE-III) GT1b patients who received 3-DAA alone. Thresholds of 1 and 15%, respectively, detected the prevalence and impact of baseline RAVs; impact of RAVs conferring ≥ 5-fold resistance to components of the 3-DAA regimen on response was determined by com-

paring SVR rates in patients with or without RAVs.
Results: SVR rates were 96% and 100% in patients with GT1a and GT1b, respectively. One or more NS5A RAVs were present in 11% of treatment-experienced or cirrhotic GT1a patients, whereas NS5A RAVs were found in 19% of GT1b patients (15% threshold). Similar SVR rates were seen in GT1a patients with or without NS5A RAVs. All GT1b patients with NS5A RAVs, including at position Y93, achieved SVR. NS3 RAVs were uncommon (≤2%). NS3 RAVs were not seen in any of the 14 virologic failures and an NS5B RAV was seen in 1 virologic failure. The presence of the GT1a NS3 Q80K polymorphism had no impact on SVR.
Conclusions: Understanding impact of baseline NS5A RAVs on treatment outcomes is important for relevant HCV therapies. Patients with HCV GT1a-infection treated with the 3-DAA regimen + RBV achieved high SVR rates, regardless of the presence of baseline RAVs. All GT1b patients treated with the 3-DAA regimen alone achieved SVR.
Keywords: HCV GT1, Resistance-associated variants, Ombitasvir/paritaprevir/ritonavir + dasabuvir

PO-010

Real-life Prevalence of Resistant Associated Variants (RAV) and Early Treatment Response of Daclatasvir Plus Asunaprevir Combination Therapy

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Aims: Daclatasvir plus asunaprevir (DCV+ASV) has been approved in Korea for the treatment of genotype 1b chronic hepatitis C (CHC) infection since August 2015. Being the firstly approved all-oral regimen in Korea, DCV+ASV regimen has been used popularly in Korea although the response to DCV+ASV is known to depend on the existence of resistant associated variants (RAV) against DCV, NA5A inhibitor. We investigated the real-life prevalence of RAV against NA5A inhibitor in HCV 1b patient and response of DCV+ASV treatment in a single referral hospital.
Methods: Patients with CHC genotype 1b who underwent prescreening examination before the initiation of DCV+ASV at Gangnam Severance Hospital from August 2015 to April 2016 were enrolled.
Results: Total 137 patients (male 49, female 88) were tested for RAV before the treatment. The average age of the patients was 57.7. (30-90). Liver cirrhosis was found in 32.8% (45/137) patients, and 16.0% (22/137) patient had previous experience of interferon based treatment. Of 137 patients, 26 patients (18.9%) showed RAV positive. The rate of RAV positivity was not different between treatment-naïve and treatment experienced (TE) patients. Incidence of positive RAV was not affected by the existence of liver cirrhosis. Among 111 patients without baseline NS5A RAVs, 70 patients underwent DCV+ASV treatment. Rapid virologic response (RVR) at week 4 after the initiation of DCV+ASV was evaluated in 60 patients. Those who did not undergo RVR evaluation were the one with progressed HCC, another with lost follow up, and the other stopped the treatment due to serious drug side effect (thrombocytopenia). Other 7 patients have not reached week 4 after the treatment, yet. Among those who had RVR evaluated, 98.3% patients achieved RVR at week 4 (59/60). Among the patients that achieved RVR, 36 patients completed 24 weeks of the treatment. All of these patients with RVR achieved HCV RNA negative at the end of the treatment (29/29, 100%).
Conclusions: In our real-life data, 18.9% (26 of 137) of patients with CHC genotype 1b infection showed RAV positive against NS4A inhibitor. Patient with RAV negative who received treatment with DCV+ASV showed high RVR rates, and we are expected to achieve sustained virologic response.
Keywords: HCV, Daclatasvir, Asunaprevir, DAAs

PO-011

One of the Earliest HCV Treatment Results with Direct Acting Antiviral Agents

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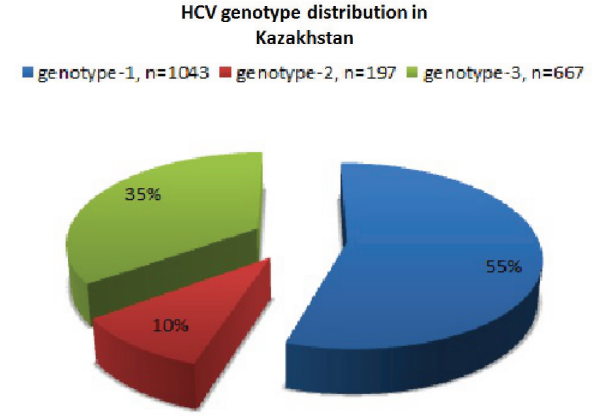
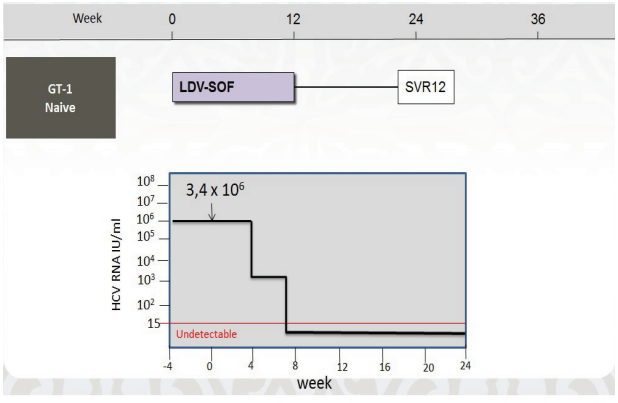
Aims: The aim of this case report is to present a successful treatment of hepatitis C infection in a cirrhotic patient with a new direct acting antiviral regimen.
Introduction: Kazakhstan has a high burden of end stage liver diseases and anti-HCV prevalence varies from 3.2% up to 4.6% according to screening programs conducted in different areas of the country. According to the data presented by Hepatology centers were they conduct free governmental supported IFN+RBV treatment genotype





1 accounts for more than 50% of cases (figure-1: HCV genotypes). The introduction of new antiviral regimens for HCV-infection is expected to decrease the disease burden in Kazakhstan, especially in those hard to treat population including genotype-1 non-responders.

Methods: A case report study is based on clinical observation of the patient. A 59 y.o. female from Southern Kazakhstan presented with chief complain of pain in the RUQ, decreased appetite, fatigue, and dyspepsia. History of present illness: abovementioned symptoms started 1-2 years ago, treated for the dyspepsia with PPI (omeprazole), antacids. Past history: 4 kids, natural delivery, no blood transfusion (or cannot remember of any). Had dyspepsia treatment for years (sanatorium and private clinics). Family history: no viral hepatitis among family members or liver diseases.

Results: Complete blood count was remarkable for low platelet count (PLT - 113 x 109/L), all other parameters were within the normal ranges (WBC - 7,89 x 109/L, Hb - 149 g/L, HCT - 41.9%, RBC - 4,63 x 1012/L, PLT - 113 x 109/L, LYMF - 28/6%, Ne - 60.6 %). Coagulation: PT - 12,8sec, APTT - 28,2 sec, fibrinogen - 1,3 g/L (1,8-3,5), PT by Quick - 74,5%, INR - 1,03. Liver enzymes slightly elevated (ALT - 88,6 U/L, AST - 66,4). Other indicators were unremarkable or were slightly changed (TB - 13 mkmol/L, Total protein - 73,8 g/L, Albumin 43,4 g/L, Glucose - 5,37, Creatinine - 51 mkmol/L, Ferritin - 179,7 ng/ ml, Serum Fe - 19,34, AFP - 5,6, Total cholesterol - 4,8 mMol/L, TGC - 0,77 mMol/L). Antibodies for HBsAg - negative, Anti - HCV - positive, PCR (HCV - RNA) qualitative came positive with viral load 3.4x106/L, genotype - 1. GI endoscopy revealed esophageal varices stage 0-1, reflux esophagitis. Elastometry showed advanced fibrosis F4 by METAVIR, ECG showed no bradicardia, no arythmia in the past and current times. She was confirmed with a diagnosis of Chronic HCV induced Liver Cirrhosis, Child A-5. Portal hypertension: esophageal varices stage 0-1, splenomegaly and thrombocytopenia.

The patient agreed to start on sofosbuvir 400mg + ledipasvir 90mg regimen for 12 weeks. Advised to exclude antacids and PPI's for the duration of this treatment. As shown in the figure-2 (HCV-RNA) the viral load dropped 3 logs after 4 weeks from the initiation of therapy, the following 8 and 12 week assessment were negative for HCV- RNA, and patient cleared the virus (SVR 12). In the follow up lab results liver enzymes normalized, inflammation markers were decreased and the long-term effects of the treatment success will be tracked.

Conclusions: This case report represents the importance of treatment of HCV-infection in a patient with a compensated cirrhosis to stop the progression of the end stage liver disease and delay the liver transplantation.

I have no conflict of interests in this case report.

Keywords: HCV, Liver cirrhosis, DAA, Genotype 1

PO - 012

Efficacy of Daclatasvir + Asunaprevir for Patients with Chronic HCV Genotype Ib Infection

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Aims: The combination of daclatasvir (DCV) and asunaprevir (ASV) has demonstrated high SVR and low adverse event rate in clinical studies. The purpose of this study is to clarify the results of treatment and side effects in Korean patients.

Methods: We retrospectively analyzed the clinical data of chronic HCV genotype Ib patients who treated with DCV (60mg QD) + ASV (100mg BID) between August 2015 and April 2016 at 5 hospitals. The rate of resistant associated variants (RAV), SVR12, adverse events were assessed.

Results: Total 152 patients (male; 62, female; 90) got the examination for RAV. Among them, 15 patients (9.9%) showed positivity in Y93 and 1 patient (0.7%) showed positivity in L31. 126 patients (male; 52, female; 74) were treated with DCV + ASV and 8 patients (6.3%) was positive in Y93. 35 patients (27.8%) had cirrhotic change. This treatment was first therapy to 95 patients (75.4%). 20 patients (12.7%) and 15 patients (11.9%) was relapsed after previous treatment including interferon and intolerant to interferon, respectively. Adverse events such as liver enzyme elevation (2), GI discomfort (4), itching or skin rash (4), generalized weakness (2) were found on 10 patients (7.9%). 2 patients stopped the medication because of severe itching sensation and skin rash. Total 59 patients finished the 6 months treatment and 4 patients (6.8%) showed treatment failure. Among 4 patients, 1 relapsed and 1 Y93 positive patient was included. 38 patients who visited at 3 months after treatment showed all SVR12.

Conclusions: DCV + ASV treatment revealed good treatment efficacy in patients with chronic hepatitis C in Korea. But close monitoring was needed for severe adverse event and treatment failure although they were found in a few patients.

Keywords: Daclatasvir, Asunaprevir, Chronic hepatitis C

Liver Cirrhosis

PO - 013

Role of New Biomarkers in Predicting AKI in Patients with Advanced Liver Cirrhosis

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Aims: Acute kidney injury is known to be common and have poor prognosis in cirrhotic patients. Although early, accurate detection of AKI in these patients may allow more targeted therapy, current diagnostic criteria using serum creatinine or urine output lacks sensitivity in early prediction. The purpose of this study is to examine

the prognostic performance of urinary biomarkers in early prediction of AKI in cirrhosis.

Methods: This is a single center, prospective cohort study enrolling cirrhotic patients who admit to Hallym University Kangnam Sacred Hospital due to diverse etiologies. Urine was collected for measurement of urinary neutrophil gelatinase associated lipocalin (NGAL), liver type fatty acid binding protein (L-FABP) and patients' clinical outcome was prospectively collected.

Results: Of 41 patients, AKI developed in 16 patients during the hospital admission (39%). AKI was associated with higher in hospital mortality (AKI vs. non-AKI, 25% vs. 8%, $p < 0.05$). Etiologies for admission, prior use of diuretics, initial serum creatinine (0.78±0.53 vs. 0.73±0.58 mg/dL), fractional excretion of sodium (FENa, 0.28±0.07 vs. 0.15±0.17 %), fractional excretion of urea (FEurea, 10.3±4.8 vs. 18.9±11.4 %) were not different between AKI and non-AKI cirrhotic patients. However, baseline Model for End stage liver disease score (MELD score, 18.4±6.3 vs. 13.5±7.2, p=0.027), initial plasma NGAL (219±105.7 vs. 88±47.1 ng/mL, p=0.016), urinary L-FABP (12.9±7.6 vs. 7.7±6.72 ng/mL, p=0.05) were significantly higher in patients who subsequently developed AKI.

Conclusions: This ongoing study shows that the incidence of AKI is high and portends poor prognosis in cirrhotic patients. High MELD score, plasma NGAL and urinary FABP might be useful biomarkers for early detection of AKI in cirrhosis.

Keywords: Advanced Cirrhosis, AKI, Biomarker, Prognosis

PO - 014

Comparison of Prognostic Efficacy of Acute Kidney Injury Criteria in Patients with Liver Cirrhosis

Tae Hyung Kim, Yeon Seok Seo, Seung Woon Park, Han Ah Lee, Sang Jung Park, Sang Jun Suh, Young Kul Jung, Ji Hoon Kim, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um

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Aims: Development of acute kidney injury (AKI) is closely associated with mortality in patients with liver cirrhosis. Recently, several new definitions of AKI were published. This study was performed to compare the efficacy of several definitions of AKI for predicting prognosis in cirrhotic patients.

Methods: Cirrhotic patients who hospitalized to our hospital were enrolled. Patients with hepatocellular carcinoma and parenchymal kidney disease were excluded. AKI was defined by conventional, RIFLE, and KDIGO criteria.

Results: A total of 696 cirrhotic patients were enrolled. Age was 54.1±10.7 years and 526 patients (75.6%) were men. Child-Pugh and MELD scores were 8.7±2.4 and 15.5±6.9, respectively. During follow-up, 155 patients died. Six and 12 months mortality rates were 10.7% and 14.2%, respectively. Among all patients, 22 (3.2%), 29 (4.2%), and 52 (7.5%) patients fulfilled the criteria of AKI of conventional, RIFLE, and KDIGO definitions, respectively. Survival time differed significantly between patients without and with AKI according to the conventional (92.3±2.1 vs 18.7±6.2 months, P<0.001), RIFLE (92.3±2.2 vs 42.8±11.2 months, P<0.001), and KDIGO (94.0±2.2 vs 44.0±8.3 months, P<0.001) criteria. Both conventional and KDIGO criteria were fulfilled in 22 patients (3.2%), while 30 patients (4.3%) fulfilled only KDIGO criteria. There was a trend of worse prognosis in patients who fulfilled both conventional and KDIGO criteria than those who only fulfilled KDIGO criteria (18.7±6.2 vs 53.3±11.1 months, P=0.051). Both RIFLE and KDIGO criteria were fulfilled in 29 patients (4.2%), while 23 patients (3.3%) fulfilled only KDIGO criteria. Survival did not differ between patients who fulfilled both RIFLE and KDIGO criteria and those who fulfilled only KDIGO criteria (42.8±11.2 vs 30.1±7.7 months, P=0.106).

Conclusions: KDIGO criteria for AKI predicted survival in cirrhotic patients more accurately compared to conventional and RIFLE criteria. Our results suggest that even subtle changes in the serum creatinine level requires close attention in these patients.

Keywords: Liver cirrhosis, Acute kidney injury, Prognosis

PO - 015

Baseline Renal Function Predict Hyponatremia in Liver Cirrhosis Patients Treated with Terlipressin for Variceal Bleeding

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Aims: Terlipressin is safely used for the management of acute variceal bleeding. However, side effects, such as hyponatremia, although very rare, can occur. We investigated the development of hyponatremia in cirrhotic patients who had acute variceal bleeding treated with terlipressin, and attempted to identify the risk factors associated with the development of hyponatremia.

Methods: This retrospective, case-control study investigated 88 cirrhotic patients who developed hyponatremia and 116 control subjects who did not develop hyponatremia and were matched in terms of age and gender during same period following terlipressin administration.

Results: The overall change in serum sodium concentration and the mean lowest serum sodium concentration were 3.44±9.55 and 132.44±8.78 mEq/L during treatment, respectively. In 47 patients (53.5%), the serum sodium level decreased by 5-10 mEq/L; in 20 patients (22.7%), this level decreased by 10-15 mEq/L; and in 21 patients (23.8%), this level decreased by >15 mEq/L. Multivariate analysis revealed that baseline normal or near-normal serum sodium and creatinine levels were independent positive predictors of the development of hyponatremia. The presence of HBV, DM, and shock on admission were independent negative predictors of the development of hyponatremia (P <0.05). The strongest predictor of the development of hyponatremia after terlipressin treatment was the baseline serum creatinine level (odds ratio, 0.166; 95% confidence interval, 0.067-0.412; P <0.001).

Conclusions: Hyponatremia after terlipressin treatment may be developed in cirrhotic patients with relatively preserved liver function and renal conditions. Physicians conduct vigilant monitoring to prevent the possible neurological complications associated with severe hyponatremia.

Keywords: Esophageal and gastric varices, Hyponatremia, Liver cirrhosis, Terlipressin

PO - 016

Increased Risk of Bacterial Infection in Cirrhotic Patients with Acute Variceal Bleeding Who Were Treated with Prophylactic Rifaximin

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Aims: Prophylactic antibiotic use for spontaneous bacterial peritonitis or hepatic encephalopathy is common in decompensated cirrhotic patients with low level of ascitic protein and poor liver function. There is controversy whether prolonged antibiotic use is related with increased risk of bacterial infection other than SBP. We investigated whether the prophylactic use of rifaximin is associated with increased infection risk in cirrhotic patients.

Methods: We reviewed the charts of 160 cirrhotic patients with acute variceal bleeding between 2009 and 2015 and compared the use rate of prophylactic rifaximin in infection group and non-infection group within 1, 3, and 6 months off-treatment.

Results: Among 160 patients, 105 patients developed bacterial infection within a year follow-up. Ironically the rate of rifaximin use was higher in the infection group than non-infection group in 1, 3, 6 months off-treatment ($p<0.001$). MELD score were similar in both groups of patients. Prophylactic rifaximin was the only independent predictor of infection in 1 and 3 months off-treatment and odd ratios (OR) were 8.00/5.00 for 1month ($p<0.001$)/3months ($p<0.001$). Thrombocytopenia (OR 0.992, $p=0.009$) and rifaximin use (OR 2.963, $p=0.002$) were predictors of infection in 6 months off-treatment. However, types of infection were not significantly different between two groups.

Conclusions: Prophylactic use of rifaximin after intravenous antibiotics in cirrhotic patients with acute variceal bleeding increased the risk of bacterial infections. Further study about gains & losses of prophylactic rifaximin are needed, especially in patients with various types of developed infection.

Keywords: Rifaximin, Antibiotics, Bacterial infection, Cirrhosis

PO - 017

Cyanoacrylate Injection versus Band Ligation for the Treatment of Bleeding from Cardiac Varices on Lesser Curvature Side of the Stomach

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Aims: Practice guidelines recommend endoscopic band ligation (EBL) for the treatment of bleeding from cardiac varices on lesser curvature side of the stomach (CVs). However, endoscopic variceal obturation (EVO) using cyanoacrylate has been reported more effective than EBL for fundal variceal bleeding and considering that the mucosa covering cardiac varices is more thickened than esophageal varices and being exposed to gastric acids or food materials continuously, EVO could be more effective than EBL for the treatment of bleeding from CVs. This study was performed to compare the efficacy between EVO and EBL for the treatment of bleeding from CVs.

Methods: All patients who were treated EBL or EVO for bleeding from CVs were enrolled. The patients diagnosed with hepatocellular carcinoma or treated with endoscopic injection therapy were excluded.

Results: A total of 77 patients treated with bleeding from CVs were enrolled. Age was 56.4±10.6 years and 67 patients (87.0%) were men. Fifty-one and 26 patients were treated with EBL and EVO, respectively. Hemostasis were achieved in 73 patients (94.8%). Hemostasis rates did not differ between EBL (47 patients, 92.2%) and EVO (26 patients, 100%) groups. Varices rebled in 13 patients during follow-up. Rebleeding rate was significantly higher in EBL group compared to EVO group ($P=0.044$). During follow-up, 12 patients died (10 in EBL group, 2 in EVO group). Mean survival time was 310.4±13.5 days, which did not differ between two groups ($P=0.142$).

Conclusions: Hemostasis success rate and survival did not differ between the EBL and EVO groups. However, rebleeding rate was significantly lower in EVO group compared to EBL group. EVO could be better option for the treatment of bleeding from CVs on lesser curvature side of the stomach.

Keywords: Varices, Endoscopy, Cyanoacrylate, Band ligation

PO - 018

Efficacy and Safety of Endoscopic Variceal Obliteration (EVO) vs. Balloon-occluded Retrograde Transvenous Obliteration (BRTO) as Prophylactic Treatment for Gastric Varices

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Aims: No single effective method has yet been established for the prophylactic treatment of gastric varices. So, we aimed to compare two prophylactic treatment methods, including EVO and BRTO for gastric varices.

Methods: We retrospectively analyzed patients with gastric varices, who had undergone either EVO or BRTO as a prophylactic treatment. The end points were eradication rate of gastric varices and gastric variceal bleeding rate during the follow-up period.

Results: Total 84 patients were consisted of 55 patients in EVO group and 29 patients in BRTO group. No difference was observed in the clinical profiles of patients, including age, gender, Child-Pugh score,

etiology of liver cirrhosis, and presence of hepatocellular carcinoma, between the EVO and BRTO groups. There was also no difference with respect to endoscopic features of gastric varices including F-component and location. As primary end points, the gastric varices were disappeared partially or completely in 50 patients in EVO group, and 27 patients in BRTO group. (90.9% vs 93.1%, p= 0.542). At the complete eradication rate, there was also no difference between two groups. (49.1% vs 65.5%, p=-0.150) However, 12 patients in EVO group bled from gastric varices after treatment during the median follow-up of 28 months, compared to only one case in BRTO group. (21.8% vs 3.4%, p=0.027) In addition, there were no differences in worsening in the endoscopic classification of esophageal varices or amounts of ascites. All-cause mortalities were similar in both.
Conclusions: EVO and BRTO are equally effective for eradication of gastric varices with similar frequencies of complications and mortalities. However, BRTO proved more effective in preventing bleeding from gastric varices in the long run.
Keywords: Balloon-occluded retrograde transvenous obliteration, Endoscopic variceal obliteration, Gastric varix

NAFLD

PO - 019

The Association between Serum Lysyl Oxidase Homolog 2 Levels and Liver Fibrosis Stages in Subjects with Non-alcoholic Fatty Liver Disease

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Aims: Lysyl oxidase homolog 2 (LOXL2), which promotes cross-linking of collagen in pathological stroma, is considered a core driver in fibrosis. Thus, LOXL2 blockage may be an effective strategy for regressing liver fibrosis in subjects with chronic liver disease. We investigated whether baseline serum LOXL2 levels would be associated with initial fibrosis stages, and would predict fibrosis progression as assessed by ARFI.
Methods: One hundred sixty-eight patients with biopsy-proven NAFLD were included in this prospective analysis. All patients underwent acoustic radiation force impulse elastography (ARFI) and serum LOXL2 quantification (ELISA). Follow-up ARFI at one year after liver biopsy was performed to assess fibrosis progression in only 100 among the 168 patients with NAFLD.
Results: The AUROC for diagnosing advanced fibrosis (≥F3) was 0.631 (optimal cut-off, 1.333; sensitivity, 75.86%; specificity, 51.08%), while that for diagnosing cirrhosis was 0.662 (optimal cut-off, 1.409; sensitivity, 81.25%; specificity, 55.26%). The AUROCs of serum LOXL2 levels were significantly lower than those of ARFI (AUROC=0.863, p <0.001 for ≥F3; AUROC=0.879, p=0.002 for F4). The AUROCs for predicting fibrosis stage improvement was 0.521 (optimal cut-off, 1.07; sensitivity, 32.29%; specificity, 100.00%), while those for predicting fibrosis progression was 0.560 (optimal cut-off, 1.691; sensitivity, 62.50%; specificity, 69.57%).
Conclusions: There was a positive correlation between baseline serum LOXL2 levels and initial liver fibrosis stages in patients with NAFLD. However, serum LOXL2 level was not accurate enough to predict the evolution of fibrosis stage as assessed by liver elastography.
Keywords: Sonoelastography, Pathology, Fatty Liver, Liver Cirrhosis

PO - 020

FOXA2 Overexpression Promotes Hepatic Differentiation of Adipose Tissue Derived Stem Cells

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Aims: We used non-viral vector gene delivery system and three dimensional culture using scaffold to increase the efficacy of hepatocyte differentiation.
Methods: The adipose derived stem cells (ADSCs) were isolated from human adipose tissue. Using microporator, Foxa2 was over-expressed in ADSCs and cultured in poly-lactic-co-glycolic acid (PLGA) scaffold. Later, for hepatic differentiation ADSCs were pre-cultured in IMDM with 20 ng/mL epidermal growth factor and 10 ng/mL fibroblast growth factor-basic (bFGF). After 2 days, the cells were cultured in Step-1 differentiation medium consisting of IMDM with 20 ng/mL hepatocyte growth factor (HGF), 10 ng/mL bFGF, and nicotinamide 0.61 g/L for 7 days. Finally, the cells were cultured in Step-2 differentiation medium consisting of IMDM with 20 ng/mL oncostatin M, 1 mol/L dexamethasone, and 50 mg/mL ITS+ premix for 7 days. For in vivo experiments, Foxa2 over-expressed ADSCs cultured in IMDM with 20 ng/mL EGF and 10 ng/mL bFGF and were loaded in scaffold for 1 day and later were implanted in nude mice dorsum for 2 weeks. After 2 weeks the scaffold was retrieved from mice. After differentiation, periodic acid-Schiff (PAS) staining, and qPCR gene evaluation were performed.
Results: After hepatic differentiation, Foxa2 over-expressed ADSCs increased the gene expression of hepatocyte-specific gene markers (alpha-fetoprotein [AFP], Cytokeratin 18 [CK18], Albumin[ALB]) in 2D cultures. In 3D cultures, Foxa2 over-expressed ADSCs increased the gene expression of hepatocyte-specific gene markers (AFP, CK18). In 2D, 3D cultures, Foxa2 over-expression increased glycogen storage ability in hepatic differentiated cells. In vivo experiments showed that after 2 weeks scaffold implant, the mRNA expression for AFP and CK18 increased in foxa2 over-expressed group while ALB expression remained the same as in vector group. Moreover, PAS staining was more pronounced in Foxa2 group.
Conclusions: Foxa2 promotes hepatic differentiation by increasing AFP, ALB and CK18 expressions in 2D, while increasing AFP, and CK18 expressions in 3D culture and in vivo system.
Keywords: Foxa2, ADSC, Hepatic differentiation, Scaffold

PO - 021

The Relationship between NAFLD and the Risk of Obstructive Sleep Apnea

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Aims: In several studies using animal models, chronic intermittent hypoxia was associated with severe liver damage in diet-induced fatty liver. Intermittent hypoxia induced by obstructive sleep apnea (OSA) is a potential risk factor of nonalcoholic fatty liver disease (NAFLD). The aim of this study was to investigate the relationship between OSA and NAFLD in non-obese patients.

Methods: We assessed the OSA risk using Berlin questionnaire (BQ) in 1612 patients who visited health promotion center in our hospital. We excluded subjects with any other liver disease including HBV or HCV hepatitis, a history of malignancy, disorders of biliary tree, alcohol intake ≥20g/day and missing biochemical and radiologic data. We also excluded subjects with BMI ≥28 kg/m2. The total number of eligible subjects for this study was 207. The severity of fatty liver was measured with liver/renal echogenicity ratio (hepatorenal index). Steatosis combined with ALT level more than 30 IU/L was defined nonalcoholic fatty liver damage, while steatosis combined with ALT level less than 30 IU/L was defined simple steatosis.

Results: Steatosis with hepatorenal index more than 1.49 was observed in 49 patients (23.8%). Of patients with steatosis, 25 (52.0%) had simple steatosis and 24 (48%) had nonalcoholic fatty liver damage. Of all 207 subjects, 134 patients (64.7%) were classified as low risk of OSA and 73 patients (35.3%) were classified as high risk of OSA through the BQ. Serum ALT level was significantly higher in subjects with high risk of OSA compared to low risk of OSA (mean ALT±SD, 31.25±20.06 IU/L vs. 22.55±14.48 IU/L, P<0.001). Also, hepatorenal index was higher in patients with high risk of OSA compared to low risk of OSA (mean±SD, 1.45±0.44 vs. 1.20±0.36, P<0.001). The number of patients with steatosis by hepatorenal index was 32 (43.8%) in high risk of OSA group and 17 (26.1%) in low risk of OSA group (P<0.001). The rate of patients with steatosis and elevated ALT level was significantly higher in high risk of OSA group compared to low risk of OSA group (14.7% vs. 4.5%, P<0.001). BMI was higher in patients with high risk of OSA than in patients with low risk of OSA (24.57±2.18 vs. 23.19±1.96, P<0.001). High risk of OSA remained correlated with the severity of steatosis (OR 1.92; 95% CI, 1.179 to 3.127; P=0.003) after adjusting for BMI.

Conclusions: In patients with BMI < 28 kg/m2, a proportion of steatosis is more frequent in subjects with high risk of OSA. NAFLD is associated with high risk of OSA regardless of BMI in non-obese patients.

Keywords: NAFLD, OSA, Hepatorenal index

PO - 022

Evaluation of Hepatic Metabolite Changes for Differentiation between Non-alcoholic Steatohepatitis and Simple Hepatic Steatosis Using Long Echo-time Proton Magnetic Resonance Spectroscopy

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Aims: To study the hepatic metabolite difference between patients with non-alcoholic steatohepatitis (NASH) and simple hepatic steatosis, and study the diagnostic accuracy of proton magnetic resonance spectroscopy (1H-MRS) with long echo-time (TE).

Methods: The local institutional review board approved this study and waived written informed consent. ^{1}H-MRS measurements were performed on a localized voxel of the liver using a point-resolved spectroscopy sequence and hepatic metabolites of the alanine (Ala), lactate/triglyceride (Lac/TG), and TG were analyzed in patients with NASH (n=11), simple steatosis (n=15), and healthy controls (n=6). The group difference was tested with the ANOVA and Tukey's post-hoc tests, and diagnostic accuracy was tested by calculating the area under the receiver operating characteristics (ROC) curve. The values of metabolites were correlated with the histopathology and non-alcoholic fatty liver disease (NAFLD) activity scores.

Results: Patient with NASH showed significant elevated the Ala ($p<0.001$), Lac/TG ($p<0.001$), TG ($p<0.05$) concentration when compared with patients who had simple steatosis and healthy controls. The patients with NASH were significantly higher than simple steatosis in Ala (mean± standard deviation, 52.5±8.3 vs 2.0±0.9; $p<0.001$), Lac/TG (824.0±168.2 vs 394.1±89.8; $p<0.05$). The area under the ROC curve to distinguish NASH from simple steatosis was 1.00 (95% confidence interval; 0.1.0, 1.00) with Ala and 0.782 (95% confidence interval; 0.61, 0.96) with Lac/TG. The Ala and TG levels were well correlated with steatosis grade, lobular inflammation, and NAFLD activity scores.

Conclusions: Non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH); ^{1}H MR spectroscopy (^{1}H MRS); hepatic metabolites.

Keywords: Non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), ^{1}H MR spectroscopy (^{1}H MRS), hepatic metabolites.

PO - 023

Sarcopenia Is a Risk Factor for Biopsy-proven Non-alcoholic Steatohepatitis or Significant Fibrosis in Non-alcoholic Fatty Liver Disease

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Aims: We explored whether sarcopenia affects the histological severity of non-alcoholic fatty liver disease (NAFLD), especially non-alcoholic steatohepatitis (NASH) and significant fibrosis, among subjects with histologically confirmed NAFLD.

Methods: The appendicular skeletal muscle mass (ASM) was measured using bioelectrical impedance analysis. Sarcopenia was defined as ASM/body weight (ASM%) beyond 2 standard deviations below the gender-specific mean for healthy young adults.

Results: Among 309 subjects (mean age, 53±14 years; men, 46.9%) without NAFLD, with non-NASH NAFLD, or with NASH, the prevalence of sarcopenia was 8.7%, 17.9%, and 35.0%, respectively (P <0.001). A high fibrosis stage was significantly more prevalent in subjects with sarcopenia (P <0.001); and the prevalence of significant fibrosis (≥F2) was significantly higher in subjects with sarcopenia than in those without (45.7%. vs. 24.7%; P <0.001). Based on crude analysis, sarcopenia was associated with NAFLD (odds ratio [OR], 3.81; 95% confidence interval [CI], 1.57 - 9.25); which was attenuated and became statistically insignificant after adjustment for body mass index (BMI), smoking status, diabetes, and hypertension. Among NAFLD subjects, subjects with sarcopenia were more likely to have NASH than those without sarcopenia based on multivariate analysis adjusted for age, gender, BMI, hypertension, diabetes, and smoking status (OR, 2.17; 95% CI, 1.15 - 4.11), even when also adjusted for insulin resistance (OR, 1.97; 95% CI, 1.01 - 3.87). Sarcopenia was also associated with significant fibrosis independent of BMI and insulin resistance (OR, 2.05; 95% CI, 1.01 - 4.16).

Conclusions: In this large biopsy-proven NAFLD cohort, sarcopenia was significantly associated with NASH and significant fibrosis. It suggests that sarcopenia may be an important target for interventions in the treatment of NASH and significant fibrosis in NAFLD patients.

Keywords: Hepatic steatosis, Appendicular skeletal muscle mass, Sarcopenia, Insulin resistance

Liver Cirrhosis and Others

PO - 024

S100B Expression and Interaction with the Receptor for Advanced Glycation End Products (RAGE) during Hepatofibrogenesis in Murine Model

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Aims: S100 beta (S100B), a member of Ca2+-modulated proteins, not only regulates various intracellular activities through stimulating inflammatory responses, but functions extracellularly as a ligand to interact with the receptor for advanced glycation end products (RAGE). The expression and activation of RAGE is associated with progression of chronic liver diseases. Therefore, we investigated S100B expression and its interaction with RAGE during hepatofibrogenesis in animal model using common bile duct ligation (BDL).

Methods: BDL was performed in 8-week-old male C57BL/6 mice with sham control (n=26) and BDL (n=26) groups. At week 1 and 3, hepatic fibrosis was evaluated by Sirius Red staining histologically and mRNA levels of fibrosis markers. S100B expression levels were measured by real time PCR, immunoblotting and immunohistochemistry. RAGE expression and interaction with S100B were identified by immunobloting and immunofluorescence, respectively.

Results: BDL induced noticeably periportal fibrosis and bile duct proliferation. On immunoblotting, S100B expression levels were increased by 1.6 and 2.5-fold at week 1 and 3, respectively, compared with sham (P < 0.05). S100B mRNA was likewise increased by 1.98 and 2.98-fold in BDL at each time point. In immunohistochemistry, S100B was mainly detected in the bile duct epithelial cells in both sham and BDL livers. Meanwhile, RAGE expression levels on immunoblot were increased by 1.52 and 1.59-fold at week 1 and 3, respectively, compared with sham (P < 0.05). In immunofluorescence, S100B expression in bile duct epithelial cell was confirmed by co-labelling with CK-19. On merging, its distribution was corresponded with RAGE which was also merged with α- smooth muscle actin of hepatic stellate cell specific marker.

Conclusions: S100B, mainly expressed in bile duct epithelial cells, was upregulated by BDL and interacted with RAGE during hepatofibrogenesis. It suggests that the intra- and extracellular functions of S100B may contribute to hepatofibrogenesis via RAGE .

Keywords: S100B, RAGE, Liver fibrosis

PO - 025

Risk and Outcome of Stroke in Patients with Liver Cirrhosis: Two Nationwide Studies

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Table 2. Incidence and adjusted hazard ratios of stroke in association with previous Liver Cirrhosis exacerbations by sex and age

	N	Events	PY	Incidence	HR	(95% CI)
No Liver Cirrhosis	27776	939	193140	4.9	1.00	(reference)
Liver Cirrhosis	6944	263	35301	7.5	1.75	(1.52-2.01)
Female*						
No Liver Cirrhosis	7680	224	55278	4.1	1.00	(reference)
Liver Cirrhosis	1920	67	11050	6.1	1.65	(1.25-2.19)
Male*						
No Liver Cirrhosis	10096	715	137682	5.2	1.00	(reference)
Liver Cirrhosis	5024	196	24251	8.1	1.79	(1.52-2.10)
20-39 years†						
No Liver Cirrhosis	1212	3	9100	0.3	1.00	(reference)
Liver Cirrhosis	303	4	2190	1.8	5.63	(1.13-28.0)
30-39 years†						
No Liver Cirrhosis	3716	20	28209	0.7	1.00	(reference)
Liver Cirrhosis	929	23	5961	3.9	4.74	(2.48-9.07)
40-49 years†						
No Liver Cirrhosis	6364	118	47211	2.5	1.00	(reference)
Liver Cirrhosis	1591	72	9098	7.9	2.92	(2.14-4.00)
50-59 years†						
No Liver Cirrhosis	6424	214	47001	4.6	1.00	(reference)
Liver Cirrhosis	1606	63	8486	7.4	1.57	(1.17-2.11)
60-69 years†						
No Liver Cirrhosis	5048	298	34977	8.5	1.00	(reference)
Liver Cirrhosis	1262	55	5490	10.0	1.22	(0.91-1.64)
≥70 years†						
No Liver Cirrhosis	5012	286	26822	10.7	1.00	(reference)
Liver Cirrhosis	1253	46	4076	11.3	1.27	(0.92-1.74)

PY, person-years

Full model adjusted for age, sex, low income, coexisting medical conditions, anticoagulant, anti-platelet agents, lipid-lowering agents

*Adjusted for all covariates in full model except sex

†Adjusted for covariates in full model except age

Table 4. Adjusted Odds Ratio and 95% Confidence Interval of Post-Stroke mortality and Complications

	No liver cirrhosis		liver cirrhosis			
	n	(%)	n	(%)	OR	(95% CI)*
Number	14178		7089			
Mortality	751	(5.3)	629	(8.9)	1.83	(1.63-2.05)
Epilepsy	330	(2.3)	213	(3.0)	1.30	(1.09-1.56)
Pneumonia	1286	(9.1)	665	(9.4)	1.04	(0.94-1.15)
Intensive care unit	5460	(38.5)	2932	(41.4)	1.23	(1.14-1.32)
Prolonged length of stay	13.58±21.08		12.61±15.52		0.91	(0.84-0.97)
Increased medical expenditure	3188±5624		3231±5254		1.14	(1.06-1.22)

* Adjusted for sex, age, low income, type of stroke, medical center, hypertension, mental disorder, diabetes, congestive heart failure, traumatic brain injury, COPD, ischemic heart disease, anemia, atrial fibrillation, renal dialysis, peripheral vascular disease

Aims: The association between liver cirrhosis (LC) and stroke was not completely understood. The purpose of this study is to evaluate stroke risk and post-stroke outcomes in patients with LC.

Methods: Using the Taiwan National Health Insurance Research Database, we identified 6944 adults aged ≥20 years diagnosed with LC in 2000-2005. Non-LC cohort consisted of 27776 adults randomly selected and matched by age and sex (case-control ratio=1:4). Incident events of stroke occurring after LC from January 1, 2000, through the end of 2009 were identified in the follow-up period. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke associated with LC were calculated. We conducted another nested cohort study consisted of 21267 patients with hospitalization due to stroke between January 1, 2004, and December 31, 2010. We calculated the adjusted odds ratios (ORs) and 95% CIs of 30-day mortality after stroke in patients with and without LC during admission.

Results: The incidences of stroke for people with and without LC were 7.5 and 4.9 per1000 person-years, respectively (P<0.0001). Compared to people without LC, patients with LC had increased risk of stroke (HR 1.75, 95% CI 1.52-2.01). The association was significant in both sexes. In the nested cohort study, LC was associated with post-hemorrhage mortality (OR 1.83, 95% CI 1.63-2.05) and epilepsy (OR 1.30, 95% CI 1.09-1.56).

Conclusions: Patients with LC showed higher risks of stroke and post-stroke mortality. Our findings suggest the urgency of preventing and managing LC by a multidisciplinary medical team for this specific population.

Keywords: Liver cirrhosis, Stroke, Risk, Outcomes

PO - 026

Risk Factor of Post-Polypectomy Bleeding in Early Liver Cirrhosis

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Aims: Bleeding is the most common colonoscopic polypectomy complication. However, the risk of post-polypectomy bleeding in liver cirrhosis is unknown. We aimed to investigate the incidence and risk factors of post-polypectomy bleeding after a colonoscopic polypectomy in patients with early liver cirrhosis(LC).

Methods: We performed a retrospective study of patients with early LC who underwent colonoscopic polypectomy at a single center between January 2006 and December 2015. In total, 41 patients with early LC were enrolled. We investigated the incidence of immediate PPB (IPPB) and delayed PPB (DPPB) in these patients.

Results: Among 41 patients, 36 (87.8%) were Child-Turcotte-Pugh class A, 5 (12.2%) were class B. The mean prothrombin time was 1.26 ± 0.33, and the mean platelet count was 124.87 ± 71.32 × 103/L. A total of 78 polyps in 41 patients were removed. IPPB was observed 5 (6.41 %) of the 78 removed polyps presented with mild oozing and were controlled by hemostatic procedures using endoscopic hemoclips. Both IPPB and non IPPB group, during the observation period there were no DPPB.

Conclusions: The risk of hemorrhage after polypectomy in the case of early cirrhosis of the liver did not increase significantly. However, when the size of the polyps are large, it is necessary to caution about bleeding after polypectomy.

Keywords: Bleeding, Polypectomy, Liver Cirrhosis, Colonic polyp

PO - 027

RIP3 Inhibition Promotes Steatosis in High Fat Diet Induced NAFLD

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Aims: The protective effects of RIP3 inhibition have been reported methionine & choline deficient (MCD) diet induced fibrosis and in

ethanol induced hepatic injury; however, the effects of RIP3 inhibition on high fat (HF) diet induced hepatic steatosis and fibrosis have not been evaluated.

Methods: 8-9 week old, C57BL/6 (WT) and RIP3KO mice were fed normal chow (NC), HF and MCD diets for 12 weeks. The animals were randomly divided into following groups (n=8): 1) WT-NC 2) WT-HF 3) WT-MCD 4) RIP3KO-NC, RIP3KO-HF and RIP3KO-MCD. The body weight of the animals was evaluated weekly. After 12 weeks, the animals were euthanized, and the liver and blood samples were collected. The liver to body weight ratio, H&E, serum AST, ALT and TG levels were assessed. Liver TG contents were evaluated using commercial kit. Western blot analysis for alpha-SMA, CD36, SREBP1, JNK, p-JNK, p-c-jun, p-peif2a, ATF6-alpha, MLKL, and LC3 were performed.

Results: The body weight of animals fed with HF diet increased while MCD diet fed animals decreased. The liver and body weight of RIP3KO-HF mice increased significantly as compared to WT-HF group; moreover, the liver and liver/body weight ratio was also increased in RIP3KO animals. The H&E evaluation showed significantly increased steatosis in HF and MCD diet fed groups. However, the extent of steatosis seemed to be more pronounced in RIP3KO-HF diet group. The serum AST & ALT increased in both HF and MCD diets groups; however, AST and ALT were significantly increased in RIP3KO animals in MCD and HF diet fed groups, respectively. The hepatic TG contents were also significantly increased in RIP3KO-HF group as compared to WT and RIP3KO-MCD groups.

Conclusions: RIP3 inhibition in HF diet fed animals promotes steatosis and development of NAFLD.

Keywords: Regulated Necrosis, Necroptosis, RIP3, NAFLD

PO - 028

Prevalence of Vitamin D Deficiency in Chronic Liver Disease at the Outpatient Clinics of the University of the Philippines-Philippine General Hospital

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Aims: Low vitamin D levels result in higher incidence of liver fibrosis and cirrhosis, poor treatment response, and increased morbidity and mortality in patients with chronic liver disease (CLD). This study assessed whether CLD patients in the Philippines, despite adequate sunlight exposure, have vitamin D deficiency and whether this is associated with poor outcomes.

Methods: Consecutive CLD patients at the outpatient clinics of PGH were included. Clinical data such as age, gender, body mass index, etiology of CLD, presence of cirrhosis and ascites, and number of hours of sun exposure daily were recorded. Standard biochemical liver tests within 3 months of enrolment into the study, such as alanine and aspartate aminotransferases, prothrombin time, total bilirubin, and albumin were documented. Child Pugh scores for cirrhotic patients were computed. Serum vitamin D was determined using the ARCHITECT chemiluminescent microparticle assay. STATA SE version12 for Windows was used for statistical analyses. Univariate analysis and simple logistic regression were used to determine independent predictors of vitamin D deficiency. A p-value of<0.05 was considered as statistically significant.

Results: A total of 72 patients were included. The prevalence of vitamin D deficiency (<20ng/mL) was 6.9%; insufficiency (20.1 to 29ng.mL) 52.8%; and sufficiency (>30ng/mL) 40.3%. Both univariate analysis and logistic regression showed no statistical difference among vitamin D deficient, insufficient, and sufficient subjects in terms of etiology and factors affecting the severity of CLD.

Conclusions: Vitamin D deficiency and insufficiency are prevalent in Filipino CLD subjects. Guidance on adequate sunlight exposure and dietary intake should be part of health maintenance intervention for these patients.

Keywords: Vitamin D, Chronic liver disease, Philippines

HBV, Clinical

PO - 029

Treatment Outcomes of Long-term Tenofovir based Antiviral Therapy for Patients with Chronic Hepatitis B: A Single Center, Retrospective Cohort Study

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Aims: We aimed to analyze treatment outcomes of long-term tenofovir (TDF) based antiviral therapy for patients with chronic hepatitis B (CHB).

Methods: In this single center, retrospective cohort study, we collected data from patients with CHB treated by TDF based antiviral therapy from August 2012 to October 2015. Cumulative incidence and independent risk factors for virologic response (<20 IU/mL) were analyzed by Kaplan-Meier curve and multivariable Cox regression analysis, respectively.

Results: Of total 456 patients, mean age was 48.5 years, 250 (54.8%) had a history of previous antiviral therapy, 161 (35.5%) had genotypic resistance, 378 (82.9%) treated by TDF monotherapy while 78 (17.1%) treated by TDF with other nucleoside analogues, and median duration of TDF based therapy was 23.5 (range 6-41) months. Overall, cumulative incidences of virologic response were 75.7%, 88.8%, and 89% at 12-, 24-, and 36-month). Duration of TDF therapy (HR 1.09, 95% CI 1.05-1.13, $P < 0.0001$), HBsAg $\geq$ 4log10U/mL (HR 0.22, 95% CI 0.10-0.46, $P < 0.001$), HBeAg-positive (HR 0.20, 95% CI 0.06-0.57, $P = 0.006$) and HBV DNA level at baseline (HR 0.83, 95% CI 0.70-0.98, $P = 0.026$) were independent predicting factors for virologic response by multivariate analysis. However, previous antiviral therapy, genotypic resistance, and TDF monotherapy were not sig-

nificantly associated with virologic response. During the follow-up period, HCC developed in 12 (2.6%) patients.
Conclusions: Long-term TDF based therapy is an effective strategy for achieving virologic response among CHB patients which is not significantly affected by previous antiviral therapy, genotypic resistance, and TDF monotherapy.
Keywords: Tenofovir, Hepatitis B, Virologic repsone, Treatment

PO - 030

Comparison of Long-term Efficacy of Tenofovir Monotherapy between Nucleos(t)ide-naïve and Nucleos(t)ide-resistant Chronic Hepatitis B Patients

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Aims: Tenofovir (TDF) is a nucleotide analog used in the treatment of chronic hepatitis B (CHB) infection regardless of whether nucleos(t)ide resistance. This study compared the long-term efficacy of TDF in nucleos(t)ide analog (NA)-naïve and NA-resistant chronic hepatitis B (CHB) patients.
Methods: Of the 540 eligible patients, 452 were NA-naïve and 88 were resistance to NA therapy prior to TDF rescue therapy.
Results: The median follow-up period during TDF therapy was 23.0 months (range, 6-45 months). VR occurred in 443 patients (369 patients belonged to the NA-naive group and 74 patients belonged to the NA-resistant group) during the treatment period. There was no statistically significant difference in VR between the NA-naive group and the NA-resistant group (86.8% vs. 89.4%; P = 0.802); however, the former subgroup had significantly higher baseline HBV DNA values (mean, 6.35 ± 1.40 vs. mean, 4.12 ± 1.65 log10 IU/mL for NA-naive and the NA-resistant groups, respectively, P< 0.001). ALT normalization rates also did not differ between both groups (80.0% and 63.6% in the NA-naive group and the NA-resistant group, respectively; P = 0.502). During TDF therapy, 16.4% (43 of 262) of patients in the NA-naive group, and 7.5% (4 of 53) of patients in the NA-resistant group achieved HBeAg seroconversion, respectively (P = 0.137). Multivariate logistic regression analysis using selected baseline factors identified absolute HBV-DNA levels at baseline (P < 0.001; OR, 0.671; 95% CI, 0.592-0.759), NA-resistant group (P = 0.021; OR, 1.568; 95% CI, 1.048-2.344), and HBeAg positivity (P = 0.033; OR, 1.498; 95% CI, 1.034-2.172) as factors showing significant association with VR. There were no significant clinical adverse events during rescue treatment in the NA-naive group and the NA-resistant group.
Conclusions: TDF was effective and safe for patients regardless of whether they were NA-naïve or resistant. Especially, the lower HBV DNA levels at baseline, HBeAg-negative, and NA-naïve patients were significantly associated with VR.
Keywords: Tenofovir, Nucleos(t)ide analog-naïve, Nucleos(t)ide-resistance, Chronic hepatitis B

PO - 031

Obesity and Hepatocellular Carcinoma in Patients Receiving Entecavir for Chronic Hepatitis B

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Aims: It is unclear whether or not obesity influences hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) unlike chronic hepatitis C. This study aimed to clarify the effect of obesity on the development of HCC in CHB patients receiving antiviral treatment.
Methods: This study was retrospectively analyzed based on a historical cohort in Bundang Jesaeng Hospital. A total of 102 CHB patients were treated with entecavir as an initial treatment for CHB and checked with body composition analyzer (electrical bioimpedance analysis) for obesity. Hepatic steatosis was measured semi-quantitatively using Hamaguchi's scoring system in ultrasonography. Risk factors including obesity-related factors (body mass index, waist circumference, waist-to-hip ratio, visceral fat area, and hepatic steatosis) were analyzed for HCC development.
Results: The median follow-up duration of the patients was 45.2 (interquartile range: 36.0~58.3) months. The cumulative incidence rates of HCC at 1 year, 3 years, and 5 years were 0%, 5.3%, and 9.0%, respectively. Univariable analysis revealed that the risk factors for HCC development were platelet count <120,000 /mm^2 (HR 5.21, p=0.031), HBeAg negativity (HR 5.61, p=0.039), and liver cirrhosis (HR 10.26, p=0.031). Multivariable analysis showed that the significant risk factor for HCC development was liver cirrhosis (HR 9.07, p=0.042). However, none of obesity-related risk factors were significantly associated with HCC: BMI ≥25 kg/m^2 (HR 0.90, p=0.894), waist circumference ≥90 cm (HR 1.10, p=0.912), waist-to-hip ratio ≥0.9 (HR 1.94, p=0.386), visceral fat area ≥100 cm^2 (HR 1.69, p=0.495), and hepatic steatosis (HR 0.57, p=0.602).
Conclusions: HCC development is associated with liver cirrhosis but not obesity-related factors in CHB patients receiving entecavir.
Keywords: Chronic hepatitis B, Hepatocellular carcinoma, Obesity, Antiviral treatment

PO - 032

The Effect of Tenofovir on Renal Function in Patients with Chronic Hepatitis B

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Aims: Tenofovir disoproxil fumarate (TDF) is widely used to treat

patients with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection. Despite the excellent safety records of this regimen, a few cases of acute renal failure and Fanconi syndrome have been reported among HIV patients exposed to TDF. We investigated the effect of TDF on renal impairment in patients with chronic hepatitis B.

Methods: The consecutive cohort analysis included 315 chronic hepatitis B patients (CHB) on the prescription of TDF from January 2012 to May 2016 in Soonchunhyang Seoul hospital. Analyses were further limited to 111 patients who had 1) at least 48 weeks therapy with TDF, 2) no past or concurrent use of acyclic nucleotide analogues or other nephrotoxic drugs, 3) no previous renal impairment (creatinine≤1.5mg/dL, estimated glomerular filtration rate (eGFR)≥ 60mL/min), and 4) corrected calcium, phosphate, creatinine and eGFR measured prior to therapy. Alterations over time in corrected calcium, phosphate, creatinine and eGFR were analyzed using Generalized estimating equation method and Bonferroni correction.

Results: The mean baseline creatinine, eGFR, corrected calcium and phosphate level were 0.72 ± 0.01mg/dL, 106.37 ± 1.06mL/min per 1.73m2, 8.82 ± 0.04mg/dL and 3.42 ± 0.05mg/dL. The mean creatinine level was significantly increased at 12 weeks (+0.08, P=0.00), 24 weeks (+0.10, P=0.00), 48 weeks (+0.13, P =0.00), 72 weeks (+0.14, P=0.00), 96 weeks (+0.17, P=0.00), respectively. eGFR was also significantly decreased at 12 weeks (-6.46, P=0.00), 24 weeks (-8.31, P=0.00), 48 weeks (-11.82, P=0.00), 72 weeks (-12.03, P=0.00), 96 weeks(-14.29, P=0.00), respectively. The mean corrected calcium, phosphate level were not significantly different from the baseline during therapy.

Conclusions: Renal function was decreased from the baseline in CHB patients with TDF therapy. Therefore, renal function of the patients undergoing treatment with TDF should be regularly monitored.

Keywords: Tenofovir, Chronic hepatitis B, Renal function

PO - 033

Clinical Course of Partial Virologic Responders under Prolonged Tenofovir Therapy in Nuclos(t)ides-naïve Patients with Chronic Hepatitis B

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Aims: The clinical course of patients with partial virologic response diagnosed with chronic hepatitis B undergoing tenofovir (TDF) therapy is unclear.

Methods: We retrospectively investigated the long-term clinical outcomes of TDF therapy for more than 12 months in 391 nucleos(t)ide-naive chronic hepatitis B patients, particularly those with partial virologic response (PVR; i.e., a detectable HBV-DNA level after 24 weeks of therapy).

Results: The median duration of TDF therapy was 24 months (range 12-40 months). Two-hundred twenty five (57.5%) patients were HBeAg positive. The mean pre-treatment HBV-DNA levels were 6.25 ± 1.41 log10 IU/mL. Virologic response (VR) was achieved in 341 patients (87.2%). Among 225 HBeAg-positive patients, 39 (17.3%) achieved HBeAg seroconversion. Virologic breakthrough was observed in 14 patients (3.6%). PVR was evident in 123 (31.5%) patients. During continuous prolonged TDF therapy, VR of patients with PVR was achieved in 76 (61.8%) patients. Multivariate logistic regression analysis using selected baseline factors identified absolute HBV-DNA levels at baseline (P < 0.001; OR, 0.496; 95% CI, 1.369-1.969) and HBeAg positivity (P = 0.021; OR, 0.622; 95% CI, 1.096-3.167) as factors showing significant association with PVR.

Conclusions: The vast majority of chronic hepatitis B patients in this study achieved virologic response through prolonged TDF therapy. This result suggests that adjustment of TDF therapy in patients with PVR is not necessary.

Keywords: Tenofovir, Partial virologic response, Chronic hepatitis B

PO - 034

Significant Genomic Variants Associated with Hepatitis B Surface Antigen Seroclearance in Korea

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Aims: Hepatitis B surface antigen (HBsAg) seroclearance is one of the most important goal in treatment of chronic hepatitis B (CHB). Many CHB patients were treated with diverse medication, but only a few were achieved HBsAg seroclearance. There are some studies about factors related to HBsAg seroclearance for prediction, but few studies explored in genomic level. This study aimed to reveal unique genomic variants associated with HBsAg seroclearance.

Methods: Total 200 patients were enrolled and composed of 100 patients with HBsAg seroclearance and 100 patients with high expression level of HBsAg. We collected blood samples from them, and genotyped using the Illumina HumanOmni2.5-8 BeadChip. We performed statistical analysis through chi-square test, Fisher's exact test, and logistic regression model.

Results: There were revealed available 2,344,229 single nucleotide polymorphisms (SNPs) after excluding 25,669 by missingness test and 23,027 by HWE test. The Significant 18 SNPs (P-value < 1 x 10-5) were identified: rs4915485, rs12463513, rs1558599, rs1823746, rs171941, rs9692552, rs2153442, rs4748035, rs1809862, rs7945342, rs7944135, rs12593003, rs4377248, rs7230406, rs7056538, rs34110460, rs35988962, rs3992852. Among them, 1 SNP is located on exon and 6 SNPs are located on intron.

Conclusions: We identified the most relevant SNPs in HBsAg seroclearance. Further studies are needed to validate and elicit function of SNPs. And that will open up horizons for personalized treatment in chronic hepatitis B.

Keywords: Hepatitis B, Surface antigen, Seroclearance, SNP

HBV, Clinical

PO - 035

Impact of Antiviral Therapy with Tenofovir or Entecavir on Renal Function in Patients with Hepatitis B Virus-related Cirrhosis

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Aims: The renal effects of nucleos(t)ide analogues in patients with chronic hepatitis B are controversial. We aimed to compare the impact of entecavir and tenofovir on renal function in patients with hepatitis B virus (HBV)-related cirrhosis.

Methods: We identified 353 patients who had been administered entecavir or tenofovir for HBV-related cirrhosis between December 2012 and November 2013 at Severance Hospital, Seoul, Korea. Study exclusion criteria included patients with a history of hepatocellular carcinoma within 24 months of treatment, patients that died within 24 months of treatment, patients treated for less than 24 months, patients with massive bleeding events, and patients with baseline estimated glomerular filtration rates (eGFR) below 60 mL/min. The final study group was comprised of 235 consecutive treatment-naïve patients treated with entecavir or tenofovir.

Results: Compensated cirrhosis was noted in 130 patients (80.2 %), and decompensated cirrhosis was noted in 32 patients (19.8 %) administered entecavir. Compensated cirrhosis was noted in 53 patients (72.6 %), and decompensated cirrhosis was noted in 20 patients (27.3%) administered tenofovir. The mean eGFR was 0.72 % lower in the entecavir group with compensated cirrhosis at week 96 than at baseline, and the mean eGFR was 5.37 % lower in the tenofovir group after treatment than at baseline (p value = 0.220). The mean eGFR was 5.57 % lower in the entecavir group with decompensated cirrhosis after treatment than at baseline, and the mean eGFR was 4.13 % lower in the tenofovir group after treatment than at baseline (p value = 0.778). Using multivariate analysis, significant factors associated with an increase in eGFR $\geq$ 20 % were baseline eGFR and diabetes mellitus; antiviral agents and baseline decompensation were not determined to be significant factors.

Conclusions: Treatment with entecavir or tenofovir can potentially cause renal impairment in patients with compensated and decompensated cirrhosis. We did not observe a significant difference in the degree of renal impairment between patients treated with entecavir or tenofovir; caution should be used when treating patients with either drug.

PO - 036

Long-term Efficacy of Tenofovir Therapy after Multiple Nucleos(t)ide Analogue Failure in Chronic Hepatitis B Patients

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Aims: Very limited data are available on long-tern efficacy of Tenofovir (TDF) rescue regimens in patients with multi-drug resistance (MDR). In this study, we evaluated the efficacy of TDF-based rescue therapy in chronic hepatitis B (CHB) patients after the failure of multiple nucleos(t)ide (NA) therapies. We also investigated the efficacy of TDF monotherpy versus TDF/entecavir (ETV) or TDF/lamivudine (LAM) combination therapy, types of MDR in these patients.

Methods: The study retrospectively analyzed 133 CHB patients who experienced failure with two or more NAs and who were switched to regimens containing TDF.

Results: Prior to TDF-based rescue therapy, resistance to both LAM (rt180, rt204) and ADV (rt181, rt236) was present in 51 patients, and 73 patients had resistance to both LAM and ETV (rt173, rt184, rt202, rt250). The other 9 patients had resistance to LAM, ADV, and ETV. The mean HBV DNA level at baseline was 4.35 ± 1.75 log10 IU/mL. The study subjects were treated with TDF montherapy (n=22), TDF/LAM (n=49), or TDF/ETV combination therapy (n=62) for more than 6 months. Virologic response (VR) occurred in 111 (83.5%) patients. At a median duration of 38 months of TDF treatment, the cumulative probabilities of achieving VR were 55.6%, 63.8%, 82.2%, and 88.0% at 6, 12, 24, and 36 months, respectively. The VR rates were not different between TDF monotherapy or combination therapy with LAM or ETV (log rank P = 0.197), and were not affected by types of MDR (log rank P = 0. 402). In univariate and multivariate analyses, absolute HBV DNA level at the start of TDF rescue treatment (P<0.001; OR, 0.603; 95% CI, 0.516-0.705) was only significantly associated with VR. There were no significant clinical adverse events during rescue treatment.

Conclusions: TDF was an efficient and safe rescue therapy for CHB patients after treatment failure with multiple NAs. On the current data, TDF-based combination therapy seemed to be no better than those achieved by monotherapy.

Keywords: Tenofovir, Multidrug resistance, Chronic hepatitis B

PO - 037

Long-term Lamivudine plus Adefovir Dipivoxil Therapy Dose Not Get Worse Significant Renal Function Compared to Adefovir Dipivoxil Monotherapy in Patients with Chronic Hepatitis B

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Aims: The aim of this study was to compare the renal dysfunction and hypophosphatemia between adefovir dipivoxil(ADF) plus lamivudine(LMV) therapy and ADF monotherapy in chronic hepatitis B(CHB) patients.

Methods: Between March 2005 and February 2014, 56 patients treated with 10mg/day ADF plus 100mg LMV(Group A) and 41 patients treated with 10mg/day ADF(Group B) were reviewed in our institution. We evaluated estimated glomerular filtration rate (eGFR), serum creatinine and serum phosphate level at the start of ADV plus LMV and ADF monotherapy and every 3 months.

Results: The median treatment duration was 73.6 and 80.1 months in groups A and B, respectively. Increased creatinine level(>0.3mg/dl) was seven patients in group A and one patient in Group B(12.3% vs. 2.4%, p=0.134). Decreased eGFR(>50%) was three patients in group A and no patient in group B(0% vs. 5.3%, p=0.262). Hypophosphatemia occurred 14(26.8%) patients in Group A and 11(26.8%) patients in Group B(p=0.799). Mean serum creatinine levels increased and mean eGFR decreased from baseline to end of treatment in Group A(Creatinine 0.75 ± 0.19 vs 0.87 ± 0.21mg/dl, p<0.01, eGFR 108±16 vs 94±18 ml/min p<0.01). Mean serum creatinine levels and mean eGFR were not changed from baseline to end of treatment in Group B(Creatinine 0.79 ± 0.16 vs 0.81 ± 0.16mg/dl, p=0.338, eGFR 102±17 vs 100±18 ml/min p=0.410).

Conclusions: Both long-term ADF plus LMV therapy and ADF monotherapy dose not deteriorate significant renal function. However, mild decrease in eGFR and increase of serum creatinine occurred in ADF plus LMV therapy compared to ADF monotherapy.

Keywords: Lamivudine, Adefovir dipivoxil, Renal function, Chronic hepatitis B

Table 1. Patient Baseline Characteristics

	Patient Group		
Baseline Characteristics	ADF	ADF with LMV	P value
Number of patients	41	56	
Age, years	49.9±9.5	48.3±10.0	0.436
Male sex	29/12	39/18	
Weight			
Treatment duration, months	80.1±18.0	73.6±15.7	0.068
HBeAg-positive			
Baseline serum creatinine (mg/dL)	0.79±0.16	0.75±0.15	0.245
Baseline eGFR (mL/minute)	102±17	108±16	0.083
Baseline phosphate	3.24±0.71	3.27±0.64	0.798
ALT, U/L	172.2±538.0	123.0±162.5	0.520
Total bilirubin, mg/dL	1.03±0.49	1.11±0.69	0.528
Albumin, g/dL	4.52±0.427	4.53±0.422	0.919
HBV DNA, log10 IU/mL			
Cirrhosis(%)	7(17.1)	10(17.5)	0.952
HTN	3(7.3)	7(12.3)	0.514
DM	0(0)	1(1.8%)	1.000

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen.
*Values are expressed as the mean _ standard deviation, median (range), or number of patients (%).

Table 2. Renal Function and hypophosphatemia of ADV Patients and ADF with LMV Patients: Baseline Characteristics and Outcomes

	Patients group		
	ADF	ADF with LMV	P value
Creatinine increase by >0.3	1(2.4%)	7(12.3%)	0.134
Creatinine increase by >0.5	0(0)	2(3.5%)	0.508
Creatinine increase by 0.3-0.5	1(2.4%)	5(8.8%)	0.396
eGFR decrease by >30%	1(5.9%)	6(10.5%)	0.566
eGFR decrease by 30-50%	1(2.4%)	3(5.3%)	0.638
eGFR decrease by > 50%	0(0%)	3(5.3%)	0.262
Total hypophosphatemia	11(26.8%)	14(24.6%)	0.799
Transient hypophosphatemia	8(19.5%)	9(15.8%)	0.631
Persistent hypophosphatemia	3(7.3%)	5(8.8%)	0.795

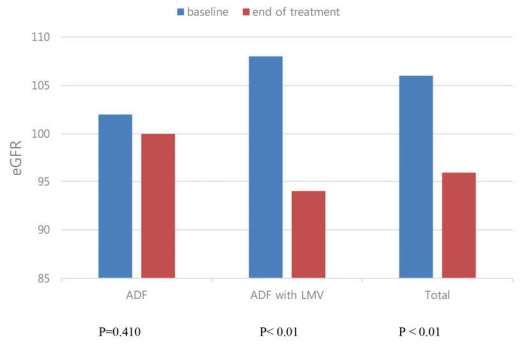

Figure 1. Decrease in eGFR in patients on ADV versus ADF with LMV patients

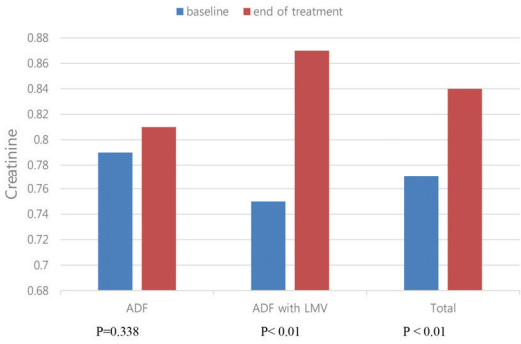

Figure 2. Increase in Creatinine in patients on ADV versus ADF with LMV patients

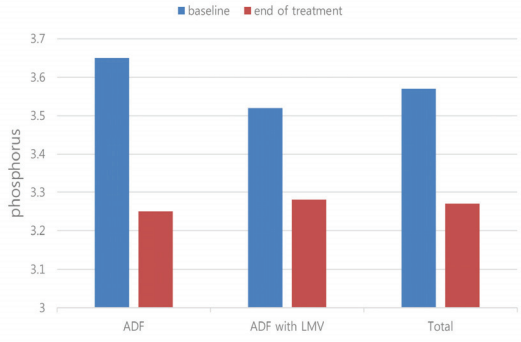

Figure 3. Decrease in phosporus in patients on ADV versus ADF with LMV patients

PO - 038

Role of FIB-4 Predicting Clinical Outcomes after HBsAg Seroclearance in Patients with Chronic Hepatitis B

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Aims: The long term clinical outcomes, including development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) after hepatitis B surface antigen (HBsAg) seroclearance in patients with high FIB-4 index remains unclear. This study aimed to determine the correlations between clinical outcomes after HBsAg seroclearance and high FIB-4 index at the time of HBsAg seroclearance in patients with chronic hepatitis B.

Methods: Between November 2000 and January 2016, a total of 117 patients who achieved HBsAg seroclearance (n=96, non-cirrhotic; n=21, cirrhotic) were retrospectively reviewed. FIB-4 index was used to evaluate the liver fibrosis. LC was diagnosed based on clinical and radiological assessments.

Results: The mean age at the time of HBsAg seroclearance was 50.1±10.5 years. Among 96 patients without evidence of cirrhosis at the time of HBsAg seroclearance, 11 (11.5%) patients developed LC. The median interval from HBsAg seroclearance to development of LC was 33 months (rage from 22 to 99 months). In univariate Cox regression analysis, platelet count (<150 x 103/mm3; HR 4.71; 95% CI 1.17-18.92; P=0.029) and FIB-4 index (≥1.70; HR 9.12; 95% CI 2.29-36.28; P=0.002) at the time of HBsAg seroclearance were significant predictive factors for development of LC after HBsAg seroclearance. During a median follow-up of 36 months after HBsAg seroclearance, HCC developed in 6 patients (5.1%) (n=3, cirrhotic; n=3, non-cirrhotic) and the 1-, 3-, and 6-year cumulative incidences of HCC were 0.9%, 2.6%, and 7.3%, respectively. The log-rank test revealed that the occurrence rate of HCC was significantly higher in the high FIB-4 index group (≥1.70) compared with that in the low FIB-4 index group (<1.70) (P=0.027).

Conclusions: Patients with a high FIB-4 index at the time of HBsAg seroclearance are at risk of development of LC and HCC, and these patients require more careful surveillance after HBsAg seroclearance.

Keywords: HBsAg seroclearance, FIB-4, Liver cirrhosis, Hepatocellular carcinoma

PO - 039

Biochemical Response Rate according to New Upper Limit of Normal ALT Level in CHB Patients Treated with Oral Antiviral Agents

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Aims: Oral antiviral agents have been main therapy for chronic hepatitis B (CHB) patients. Recently, AASLD guideline was announced and new upper limit of normal (ULN) ALT level (<19 U/L for females and <30 U/L for males) was suggested. We investigated biochemical response (BR) rate according to this ULN level.

Methods: This is a retrospective study of treatment naive CHB patients who had been treated with oral antiviral agents more than 3 years in Konkuk university hospital. BR rate according to old ULN of ALT (<40 U/L) and new BR (NBR) rate according to new ULN of ALT were calculated.

Results: Total 265 patients were included in this study. Mean age was 49 years old and 149 patients were male (56.2%). HBeAg positive patients were 158 (59.6%). Used agents were lamivudine (LMV, n=43, 16.2%), entecavir (ETV, n=215, 81.2%), tenofovir (TDF, n=6, 2.3%) and telbivudine (LdT, n=1, 0.4%). Mean treatment duration was 61 months. Virological response (undetectable HBV DNA) was achieved 56.3% at 6 months, 76.6% at 12 months, 87.4% at 24 months and 91.3% at 36 months. BR was achieved 73.8%, 80.3%, 82.4% and 86.8% at 6 months, 12 months, 24 months and 36 months each. NBR was achieved 33.5%, 42.8%, 34.5% an 48.7% at each time points.

Conclusions: Less than half of the patients could achieve NBR. Reconsidering of treatment strategy according to new ULN of ALT level is warranted. Prognosis of CHB patients according to ALT level and necessity of hepatotonics use have to be investigated.

Keywords: Chronic hepatitis B, Antiviral agent, Biochemical response, ALT

HBV, Clinical

PO - 040

Switching from Tenofovir-based Combination Therapy to Tenofovir Monotherapy: Experience of Two Centers

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Aims: Tenofovir (TDF) is a potent agent for chronic hepatitis B (CHB) and TDF monotherapy has been widely accepted for treatment of multi-drug resistance. We aimed to evaluate safety of switching to TDF monotherapy from TDF-based combination therapy.

Methods: This is a retrospective study of CHB patients who had been treated with TDF-based combination therapy and switched to TDF monotherapy after achievement of virological response (VR; undetectable HBV DNA by real-time PCR) in Konkuk university hospital and Sanggye Paik Hospital.

Results: Total 38 patients were included in this study. Median age was 51 years old and 28 patients were male (73.7%). HBeAg positive patients were 31 (81.6%). Combination types were lamivudine (LMV) plus TDF (19, 50%) and entecavir (ETV) plus TDF (19, 50%). VR duration before switching to monotherapy was median 16.1 months and monotherapy duration was median 7.5 months. Within 6 months, HBV DNA became detectable in 4 patients and one of them was related with poor compliance to antiviral treatment. Excluding one patient with poor compliance, two patients had been treated with LMV plus TDF combination therapy and one patient had been treated

with ETV plus TDF combination therapy. Resistance types before combination treatment were LMV only resistance, ETV resistance, and adefovir only resistance each. VR durations of these patients were one month, 13 months and 6 months.
Conclusions: Generally, switching to TDF monotherapy from TDF-based combination treatment was safe and effective. Some cases showed that longer consolidation therapy after achievement of VR might be required for safe switching to TDF monotherapy.
Keywords: Chronic hepatitis B, Tenofovir, Entecavir, Lamivudine, Resistance

PO - 041

Outcome of 3-year Consolidation Therapy Following Virological Response in HBeAg-negative Chronic Hepatitis B Patients Treated with Nuclios(t)ide Analogues

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Aims: The durability of response after stopping nucleos(t)ide analogue (NA) therapy in chronic hepatitis B (CHB) patients remains unknown. Although HBsAg loss is to be the ideal goal of NA treatment, it is scarcely achieved especially in HBV genotype C patients. The consolidation therapy before the discontinuation of NA is suggested to be at least one year although the ideal duration of consolidation therapy is yet to be validated. We studied the long term outcome of HBeAg negative CHB genotype C patients who discontinued NA therapy after 3 years of consolidation therapy.
Methods: We retrospectively studied the outcomes of 54 HBeAg negative CHB genotype C patients who stopped NA after 3-year consolidation therapy with virological response. Consolidation therapy was defined as NA treatment which was sustained after the first undetectable serum HBV DNA before NA discontinuation. Relapse was defined as HBV DNA >2,000 IU/mL measured twice at 6 months apart within one year, or retreatment after the initial HBV DNA elevation.
Results: NAs used at discontinuation were entercavir 0.5mg (42.6%), lamivudine (25.9%), lamivudine with adefovir (16.7%), adefovir (9.3%), clevudine (3.7%), or telbivudine (1.9%). Median follow-up from the initial therapy and from the discontinuation after 3-year consolidation therapy was 91.5 (range 45.0-197.0) and 41.5 (range 3-75.6) months, respectively. The relapse was noted in 38 (70.4%) out of 54 patients after stopping NA even with 3-year consolidation therapy. The cumulative relapse rate was 26.0% at 3 months, 41.2% at 6 months, 56.9% at 1 year, and 72.6% at 2 years. After relapse, retreatment was started in 33 out of 38 patients (86.8%). All achieved virologic response to the retreatment. More than half (28/33, 84.8%) of the relapsed patients were resumed the treatment with previous NAs. There was no significant clinical factor predicting relapse after discontinuation.
Conclusions: After 3-year consolidation therapy in HBeAg negative patients, 70.4% of patients experienced a relapse after the discontinuation of NA. This study suggests that CHB patients who discontinue therapy require close monitoring and proper retreatment.
Keywords: Hepatitis B, Treatment antiviral, Discontinuation, HBeAg negative

PO - 042

Clinical Impact of Hepatic Steatosis in Patients with Chronic Hepatitis B Infection on Tenofovir Therapy

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Aims: The impact of superimposed non-alcoholic fatty liver disease (NAFLD) is well known in patients with chronic hepatitis C, however the impact in patients with chronic hepatitis B (CHB) is less distinct. We aimed to investigate the impact of NAFLD on virologic response to tenofovir treatment with chronic hepatitis B patients.
Methods: This study was designed as a retrospective cohort study. Consecutive antiviral-naïve CHB patients who visited our hospital between December 2012 and December 2013 and started tenofovir were identified from electronic medical record system. Based on controlled attenuated parameter (CAP), patients were divided into groups with hepatic steatosis (CAP score $\geq$ 260) and without hepatic steatosis (CAP score < 260). The impact of hepatic steatosis on the virologic response to tenofovir at 46 weeks of therapy was evaluated. We also investigated cumulative probabilities of achieving virologic response (VR) in CHB with and without hepatic steatosis using Kaplan-Meier analysis.
Results: A total of 95 patients were involved in the study. Twenty eight out of 95 (28.3%) of CHB patinets had hepatic steatosis. The baseline characteristics, including age, sex, AST/ALT level, HBV DNA level and liver cirrhosis are not significantly different in both groups. However, CHB patients with hepatic steatosis had a higher body mass index ($p < 0.05$). The median duration of follow-up was 130 weeks (48-160 weeks). The VR rates in CHB patients at 46 weeks were 74.2% and 74.1% in CHB patients with and without hepatic steatosis, respectively ($p>0.05$). The cumulative probabilities of achieving VR were not significantly different in both groups ($p>0.05$).
Conclusions: The presence of hepatic steatosis had no impact on the virologic response to tenofovir treatment.
Keywords: Chronic hepatitis B, Hepatic steatosis, Tenofovir, Controlled attenuated parameter

PO - 043

Outcome of 3-year Consolidation Therapy Following HBeAg Loss in HBeAg-positive Chronic Hepatitis B Patients Treated with Nuclios(t)ide Analogues

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Aims: The durability of response after stopping nucleos(t)ide analogue (NA) therapy in chronic hepatitis B (CHB) patients remains unknown.

Although HBsAg loss is to be the ideal goal of NA treatment, it is scarcely achieved especially in HBV genotype C patients. The consolidation therapy before the discontinuation of NA is suggested to be at least one year although the ideal duration of consolidation therapy is yet to be validated. We studied the long term outcome of HBeAg positive CHB genotype C patients who discontinued NA therapy after 3 years of consolidation therapy.

Methods: We retrospectively studied the outcomes of 33 HBeAg positive CHB genotype C patients who stopped NA after achieving virological response, with HBeAg loss, and underwent 3-year consolidation therapy before stopping the treatment. Consolidation therapy was defined as NA treatment which was sustained after the first HBeAg loss with undetectable serum HBV DNA before NA discontinuation. Relapse was defined as HBV DNA >2,000 IU/mL measured twice at 6 months apart within one year, or retreatment after the initial HBV DNA elevation.

Results: NAs used at discontinuation were lamivudine (15.2%), lamivudine with adefovir (33.3%), adefovir (24.3%), clevudine (3.0%), telbivudine with adefovir (3.0%), or entercavir 0.5mg (21.2%). Median follow-up from the initial therapy and from the discontinuation after 3-year consolidation therapy was 103.0 (range 48.0-185.0) and 42.4 (range 10.8-93.7) months, respectively. The relapse was noted in 21 out of 33 patients after stopping NA even with 3-year consolidation therapy. The cumulative relapse rate was 36.4% at 3 months, 45.5% at 6 months, 54.5% at 1 year, and 64.6% at 3 years. After relapse, retreatment was started in 16 out of 21 patients (72.7%). All achieved virologic response to the retreatment. More than half (10/16, 58.8%) of the relapsed patients were resumed the treatment with previous NAs. There was no significant clinical factor predicting relapse after discontinuation.

Conclusions: After 3-year consolidation therapy in HBeAg positive patients, 63.6% of patients experienced a relapse after the discontinuation of NA. This study suggests that CHB patients who discontinue therapy require close monitoring for recurrent hepatitis and restarting treatment.

Keywords: Hepatitis B, Nucleoside analogue, Treatment, Discontinuation

PO - 044

Long-term Efficacy of Tenofovir-based Rescue Therapy for Patients with Lamivudine- and Entecavir-resistant Chronic Hepatitis B

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Aims: Tenofovir (TDF) monotherapy for 48 weeks provided a virological response comparable to that of TDF and entecavir (ETV) combination therapy in patients infected with ETV-resistant HBV. Little long-term clinical data is available regarding the optimal treatment of patients who had ETV-resistant HBV.

Methods: We evaluated the long-term efficacy of TDF-based rescue therapy in the patients with ETV resistance CHB. We also investigated the antiviral efficacy of TDF/lamivudine (LAM) or TDF/ETV combination therapy as compared to that of TDF monotherapy in these patients.

Results: Seventy three patients with ETV resistance CHB were included. The median duration of TDF therapy was 37 months (range 6-45 months). Sixty-three (86.3%) patients were HBeAg positive. The mean pre-treatment HBV-DNA levels were 4.39 ± 1.81 log10 IU/mL. Study subjects were treated with TDF monotherapy (n = 12), TDF/LAM (n = 19) or TDF/ETV combination therapy (n= 42) for more than 6 months. Virologic response (VR, HBV PCR negativity) was achieved in 63 (67.2%) patients. Of 63 patients with HBeAg-positive, 6 (9.5%) patient achieved HBeAg seroconversion. The rates of VR among the treatment groups were not statistically significant at 6 months (58.3 vs. 73.9 vs. 50.0 %), at 12 months (688.7 vs. 78.9 vs. 57.8 %), and at 24 months (84.4 vs. 100 vs. 84.2 %) in the TDF monotherapy, TDF/LAM, and TDF/ ETV combination, respectively (log rank P = 0.2). In the multivariate analysis, only lower baseline HBV DNA level remained an independent predictor for VR (OR, 0.644; 95% CI, 0.528-0.789; P< 0.001)

Conclusions: Long-term efficacy of TDF-based therapy was effective in maintaining viral suppression in patients with ETV-resistant CHB. TDF monotherapy was as effective as TDF/LAM or TDF/ETV combination therapy. Therefore, TDF mono-rescue therapy is an appropriate treatment in patients with ETV-resistant CHB.

Keywords: Tenofovir, Entecavir, ETV-resistant HBV

Alcoholic Liver Disease and Others

PO - 045

Prospective Validation of LSM Using ARFI Elastography to Predict Advanced Fibrosis and Cirrhosis Based on Metavir and Laennec Staging in Patients with Alcoholic Liver Disease

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Aims: Accurate assessment of advanced fibrosis and cirrhosis is important to predict long-term clinical outcomes in patients with alcoholic liver disease. Acoustic radiation force impulse (ARFI) elastography is one of the liver stiffness measurement (LSM) methods to assess liver fibrosis in patients with chronic liver disease. However, little is known about the correlation between LSM by means of ARFI and the severity of fibrosis in patients with alcoholic liver disease.

Methods: We conducted a prospective cohort study including 170 alcoholic liver disease patients with ongoing or prior alcohol abuse history (male > 80g/day, female > 40g/day) without any other cause of chronic liver disease. We used ARFI elastography for measuring liver stiffness and performed liver biopsy for staging fibrosis based

on the Metavir stage and the Laennec sub-classification of cirrhosis. Diagnostic measurement of serum fibrosis indices and ARFI imaging were compared with predicted significant (≥F2)or advanced (≥F3) fibrosis or cirrhosis (F4) by analyzing the area under the receiver operating characteristic (AUROC) curve.

Results: Aspartate aminotransferase to alanine aminotransferase ratio (AAR) (rs=0.35, p=0.00) aspartate aminotransferase to platelet ratio index (APRI)(rs=0.17, p=0.018), and Fib-4(rs=0.35, p=0.00) showed weak positive correlations with METAVIR stages.

ROC curve analysis identified shear wave velocity (Vs) of liver ≥ 1.34m/s (AUROC of 0.917; SE, 0.0226; 95% CI, 0.865-0.954) as the optimal cut-off for predicting significant fibrosis (≥F2). For predicting advanced fibrosis (≥F3), the optimal cut-off of Vs of liver was ≥ 1.67m/s (AUROC of 0.929; SE, 0.0210; 95% CI, 0.879-0.962). For cirrhosis (F4), the optimal cut-off value was ≥ 2.09m/s of Vs of liver (AUROC of 0.929; SE, 0.0204; 95% CI, 0.877-0.961). A tendency toward increasing liver stiffness existed in a graded manner across METAVIR stages (P<0.001).

Conclusions: In this prospective evaluation of patients with alcoholic liver disease, we suggest that ARFI elastography might be an excellent, non-invasive, diagnostic tool for predicting advanced fibrosis and cirrhosis in comparison with other noninvasive serum fibrosis indices.

Keywords: Alcoholic liver disease, ARFI, Liver fibrosis, Noninvasive tool

PO - 046

The Usefulness of Liver SPECT to Assessment of Liver Function in Patient with Cirrhosis

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Aims: It is not easy to evaluate the liver function in patient with cirrhosis although there are many methods such as Child-Pugh, MELD score, etc. We aimed to study the usefulness of liver SPECT to assessment of liver function in patient with cirrhosis and the correlation with other methods.

Methods: We enrolled patients with liver cirrhosis who were taken the liver SPECT at Dankook University Hospital from Apr. 2013 to Sep. 2015. Before regular imaging, total counts of syringe were calculated for 1 minute and after injection, remnant radioactivity counts of syringe and intravenous injection site during 1 minute were assessed so that total net injected counts (TNC) into each patient was achieved using these counts. Region of interest (ROI) in liver were drawn manually and we calculated organ specific radioactive count (OSRC) on each ROI. We got the two images (anterior and posterior side) and got the OSRC from them. Then, Absolute uptake ratio (AUR) of liver and spleen on each projection image was calculated as 100 x each OSRC/TNC. Geometric mean value (GMV) of liver and spleen was calculated as 100 x √(anterior ORSC x posterior ORSC)/TNC. Their liver functions were analyzed and compared with liver SPECT results.

Results: Total 77 patients (male 56, female 21) were enrolled and their mean age was 54.3±9.0 years old. The alcohol (84.4%) was the main cause of liver cirrhosis and followed by chronic hepatitis B (6.5%), chronic hepatitis C (5.2%), unknown (3.9%). The GMV of the liver was 11.7±5.2. GMV according to Child-Pugh class was 15.5±4.8 in class A, 12.3±4.4 in class B, 6.8±2.8 in class C, respectively. Pearson correlation coefficient between Child-Pugh score and GMV was -0.668 and showed strong correlation. Pearson correlation coefficient between MELD score, MELDNa and GMV was -0.636, -0.526, respectively.

Conclusions: GMV in liver SPECT showed good correlation with liver functions such as Child-Pugh, MELD, MELDNa score. It could be used as good method to assess liver functions in patients with cirrhosis.

Keywords: Liver SPECT, Cirrhosis, Liver function

PO - 047

Assessment of Intrahepatic Hemodynamic Change Using a Microbubble Contrast Ultrasonography Can Predict the Prognosis of Acute Hepatic Dysfunction Related with Alcoholic Hepatitis in Cirrhosis

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Aims: Acute hepatic dysfunction combined with alcoholic hepatitis by continuous alcohol intake in alcoholic cirrhosis is a common cause of acute on chronic liver failure and poor prognosis. Partially, this is related with hepatic hypo-perfusion secondary to portal hypertension (PH) and intrahepatic shunt. The hepatic vein arrival time (HVAT) assessed by microbubble contrast-enhanced ultrasonography (CEUS) has been known to have close correlation with the severity of PH and intrahepatic histological grade. We investigated the utility of HVAT in prediction of short term mortality of alcoholic hepatitis combined acute hepatic dysfunction in cirrhotic patients.

Methods: Thirty nine cirrhotic patients (male 27) with alcohol related acute hepatic dysfunction were prospectively enrolled. After an overnight fast, a bolus of contrast agent (SonoVue®) was injected into an antecubital vein and signals were recorded from the right or middle hepatic veins for analysis. HVATs were calculated as the time from injection to a sustained rise in Doppler signal 10% above baseline. HVAT study was performed within 3days after admission due to acute hepatic failure and 12weeks mortality was primary outcome.

Results: The mean Child-Pugh's score, MELD score and HVAT were 9.3 ±2.6, 19.5 ±7.9 and 11.8 ± 3.5 sec respectively. 12 weeks mortalities were developed in 9 patients. HVAT was significantly different between mortality and survival group (9.3 ± 2.0 vs. 12.6 ± 3.5 sec, P = 0.002). The area under the receiver operating characteristic curve (AUROC) was 0.787 for 12 weeks mortality. The sensitivity, specificity, positive predictive value, negative predictive value for 12 weeks mortality according to HVAT cutoff value of >11.0 sec were 88.9, 66.7, 44.4 and 95.2%, respectively. Additionally, in multivariate analysis using binary logistic regression analysis, odds ratio of HVAT > 11.0

sec for 12weeks mortality was 0.645 (Confidence Interval, 0.440 - 0.948).

Conclusions: HVAT using a microbubble CEUS could be useful method in prediction of 12 weeks short term mortality in acute hepatic dysfunction of alcoholic cirrhosis based on hemodynamic and liver histology.

Keywords: Hepatic vein arrival time, Contrast-enhanced ultrasonography, Alcoholic hepatitis, Alcoholic liver cirrhosis

PO - 048

The Prevalence of Colonic Neoplasm in Cryptogenic Pyogenic Liver Abscess: A Prospectively Enrolled

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Aims: Several studies suggested that pyogenic liver abscess (PLA) was associated with colon neoplasm. Thus, colonoscopic exam for cryptogenic PLA might present the hidden colonic neoplasm, through which the intestinal flora can transmit into the liver. However, there is no prospectively enrolled cross-sectional data for colonic neoplasm in cryptogenic PLA, yet.

Methods: The patients with PLA were prospectively enrolled in two university hospitals. Among them, in case of cryptogenic PLA, the all patients were recommended to perform the colonoscopic exam for detection of colonic neoplasm.

Results: One hundred eighty three patients with PLA were enrolled for 22 months. Among them, 101 (55.2%) patients did not have a definite cause of liver abscess at initial evaluation. The maximal diameter of the largest lesion was 5.7 (1.0-14.0) cm, and 74.3% of the patients were treated by percutaneous abscess drainage. 91% of the patients who had an identified pathogen yielded Klebsiella. Sixty two patients had colonoscopic exam, and no one have a colonic neoplasm. Fifty patients had esophagogastroduodenoscopic exam, and 9 have a gastric ulcer and one did esophageal ulcer, and another one did hemorrhagic gastritis.

Conclusions: The prevalence of colonic neoplasm among the patients with cryptogenic PLA was not as high as the previous studies. The further well-designed and large scale studies are required to confirm the association of the colon neoplasm and cryptogenic PLA.

Keywords: Cryptogenic, Pyogenic, Liver abscess, Colonic neoplasm

PO - 049

Long-term Prognosis of Cirrhotic Patients Who Survived from Acute-on-chronic Liver Failure

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Aims: This study aimed to investigate the impact of ACLF on long-term survival after surviving the ACLF events in patients with acute deterioration.

Methods: A total of 1177 acutely deteriorated patients who survived more than 3 months were consecutively collected and followed up in KACLiF study. ACLF was defined by EASL CLIF-C definition. Kaplan-Meier method was used to calculate survival.

Results: Mean duration of follow up was 18.2±9.1months. The prevalence of ACLF was 8.8%(74/838). Most common etiology of cirrhosis was alcohol(62.3%). The survival of ACLF group was shorter than no ACLF group(25.6±1.2months vs. 30.7±0.4months, p=0.013). In subgroup of 558 patients with prior decompensation, survival of ACLF group was shorter than no ACLF group (23.3±1.7months vs. 29.1±0.6months, p=0.020). However, in subgroup of 515 patients without prior decompensation, survivals were not different between groups (p=0.289).

Additionally, survivals of grade 1 and no CLIF-C ACLF patients were not different regardless of presence of prior decompensation. However, with prior decompensation, survivals of grade 2 and higher ACLF patients were shorter than grade 1 and no ACLF patients (19.3±2.6months vs. 29.0±0.6months, p=0.008).

According to etiology of cirrhosis, survivals of alcoholic patients were shorter than non-alcoholic patients(30.2±1.8months vs. 23.6±1.3months, p=0.045). In the presence of prior decompensation, the experience of ACLF had worse effect on survival in alcoholic patients than non-alcoholic patients (30.0±2.4 vs 20.1±1.8, p=0.027). However, the survivals of those patients were not different in the absence of prior decompensation.

Conclusions: Long-term mortality after survival from ACLF is dependent on the presence of prior decompensation. In the presence of prior decompensation, grade 2 and higher ACLF negatively affects survival even after recovery of ACLF. Also, effects of ACLF experience is more potent in alcoholic patients. Therefore, efforts to prevent acute decompensation and progression of organ failures may be important to improve the survival of cirrhotic patients.

Keywords: Acute-on-chronic liver failure, Liver cirrhosis, Decompensation, Survival

[Group 2] June 18, 2016 | 15:30-16:30

HCC, Basic

PO - 050

Fucoidan-induced ID1 Suppression Inhibits the In Vitro and In Vivo Invasion of Hepatoma Cells

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Aims: Hepatocellular carcinoma (HCC) is a rapidly growing tumor associated with a high propensity for vascular invasion and metastasis. Recently, we reported that fucoidan displays inhibitory effect on proliferation and invasion of HCC cells. In this study, we investigated the anti-metastatic effect of fucoidan on HCC cells and the key signal that modulates metastasis.

Methods: The anti-metastatic effect of fucoidan was evaluated in vitro using an invasion assay with human HCC cells (Huh-7, SNU-761, and SNU-3085) under both normoxic (20% O_2 and 5% CO_2, at 37 ℃) and hypoxic (1% O_2, 5% CO_2, and 94% N_2, at 37 ℃) conditions. Complementary DNA (cDNA) microarray analysis was performed to find the molecule which is significantly suppressed by fucoidan. In vivo study using a distant metastasis model by injecting SNU-761 cells into spleen via portal vein was performed to confirm the inhibitory effect by small interfering RNA (siRNA) transfection. Immunoblot analyses were used to investigate the signaling pathway.

Results: Fucoidan significantly suppressed the invasion of human HCC cells (Huh-7, SNU-761, and SNU-3085). Using cDNA microarray analysis, we found the molecule, ID-1, which was significantly suppressed by fucoidan treatment. Downregulation of ID-1 by siRNA significantly decreased invasion of HCC cells, both in vitro and in vivo (both $P < 0.05$) in a NDRG/CAP43-dependent manner. In immunoblot assay, downregulation of ID-1 by siRNA decreased the expressions of epithelial-mesenchymal transition markers including CK19, vimentin, MMP2, and fibronectin. Immunofluorescence study also revealed that actin rearrangement was inhibited when ID-1 was down-regulated in HCC cells. Interestingly, in SNU-761 cells, the ID-1 expressions under hypoxic conditions were lower as compared to those under normoxic conditions. Under hypoxic conditions, HIF-1α up-regulated NDRG-1/CAP43, while HIF-2α down-regulated ID-1, which might be a compensatory phenomenon against hypoxia-induced HCC invasion.

Conclusions: Fucoidan significantly suppressed the invasion of human HCC cells (Huh-7, SNU-761, and SNU-3085). Using cDNA microarray analysis, we found the molecule, ID-1, which was significantly suppressed by fucoidan treatment. Downregulation of ID-1 by siRNA significantly decreased invasion of HCC cells, both in vitro and in vivo (both $P < 0.05$) in a NDRG/CAP43-dependent manner. In immunoblot assay, downregulation of ID-1 by siRNA decreased the expressions of epithelial-mesenchymal transition markers including CK19, vimentin, MMP2, and fibronectin. Immunofluorescence study also revealed that actin rearrangement was inhibited when ID-1 was down-regulated in HCC cells. Interestingly, in SNU-761 cells, the ID-1 expressions under hypoxic conditions were lower as compared to those under normoxic conditions. Under hypoxic conditions, HIF-1α up-regulated NDRG-1/CAP43, while HIF-2α down-regulated ID-1, which might be a compensatory phenomenon against hypoxia-induced HCC invasion.

Keywords: Hepatocellular carcinoma, Metastasis, ID-1, Fucoidan

PO - 051

Secreted Tenascin C from Activated Hepatic Stellate Cells Promotes Epithelial-mesenchymal Transition in Hepatic Cancer Cell

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Aims: Hepatic stellate cell (HSC) plays a pivotal role in hepatocarcinogenesis through direct effects on hepatocytes and modulation of the peri-tumoral stroma and immune response. A change in HSC secretory phenotype upon activation is closely correlated with increased proliferation, migration, and invasion of hepatocellular carcinoma (HCC) cells in vitro studies. Tenascin C (TNC) is a large hexameric extracellular matrix glycoprotein and highly expressed in several solid cancer including HCC. The aim of this study was to investigate the TNC expression by activated human HSC lines and the role of TNC in metastasis of HCC cells.

Methods: Two HSC lines, LX2 and TWNT4, were stimulated with transforming growth factor-β for 48 hours and protein expression of TNC in media was evaluated with Western blot and ELISA. LX2 was transfected with TNC siRNA for 48 hours and was continued culture for 48 hours after media change. Huh7, hepatic cancer cell line, were incubated for 24 hours with conditioned media from TNC knockdown LX2. Epithelial-mesenchymal transition (EMT)-related genes expression of Huh7 were estimated by quantitative real-time reverse transcription.

Results: TNC mRNA expressions were significantly increased in stimulated LX2 and TWNT4 and TNC protein in the media were also highly expressed in both activated HSC lines. TNC knockdown was successfully observed and TNC protein level was also significantly deceased in the media from TNC siRNA transfected LX2. E-cadherin expression was significantly increased and vimentin expression was decreased in Huh7 treated with conditioned media from TNC knockdown LX2.

Conclusions: TNC expression was significantly increased in activated human HSC lines and secreted TNC from LX2 promote upregulation EMT in Huh7.

Keywords: Tenascin C, Hepatic stellate cell, Hepatocellular carcinoma, Epithelial-mesenchymal transition

PO - 052

Ursodeoxycholic Acid-induced Apoptosis of Hepatocellular Carcinoma Cells Is Mediated by the Activation of Extrinsic

Pathway Involving TNF, CD137 and HRF Signaling

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Aims: Ursodeoxycholic acid (UDCA), which increases bile flow and modulates immune response, is used for primary biliary cirrhosis. Besides, preclinical studies have shown UDCA induces apoptosis of malignant cell lines such as colon, stomach and liver cancers, implying that it could be used as an anti-cancer agent. It was also suggested that UDCA is possibly associated with lower incidence of hepatocellular carcinoma (HCC) in hepatitis C virus-associated liver cirrhosis. This study aimed to investigate the mechanism of UDCA-induced apoptosis in HCC cell lines.

Methods: A cell viability and apoptosis assay was performed in Hep3B and Huh7 cell lines, both of which produce alpha-fetoprotein (AFP). The potential apoptosis pathways were investigated using the Human Apoptosis RT(2) Profiler™ PCR Array. Western blot hybridization, RT-PCR for mRNA expression, and the inhibition assay of target genes by siRNA were performed to confirm the pathways chosen in the array study. AFP was also measured in the media.

Results: The UDCA significantly inhibited the cell proliferation, reduced AFP levels in media, and induced apoptosis in both cell lines in similar degree. The PCR array analysis showed that UDCA predominantly increased TNF, CD137 (TNFRSF9), HRF and CASP5. UDCA induced the up-regulation of CD70 (TNFSF7), FAS and FASLG in Hep3B, while not in Huh7. UDCA-induced caspases were CASP5, CASP4 and CASP7. Western blot hybridization and RT-PCR for mRNA of TNF, CD137, HRF and CASP5 supported the display analysis results of them. The activation of extrinsic pathway involving caspase-8 and -3 was also confirmed. In the knockdown study, TNF appeared to be responsible for UDCA-induced apoptosis.

Conclusions: Our results indicate that UDCA strongly induces apoptosis of HCC cells, which is mediated by TNF, CD137 and HRF signaling. These suggest that it might be used as a potential chemotherapeutic agent for the treatment of HCC.

Keywords: Hepatocellular Carcinoma, Apoptosis, Urosodeoxycholic acid, Tumor Necrosis Factor-alpha

PO - 053

Synergistic Effect of CD44 and TGF-β1 during Epithelial-mesenchymal Transition through AKT/GSK3β/β-catenin Signaling

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Aims: The character of metastatic cells is strongly correlated to epithelial-mesenchymal transition (EMT) and cell adhesion molecules such as cadherin and CD44. CD44 is a receptor for hyaluronic acid, plays a role in migration, metastasis, and invasion. Moreover, transforming growth factor beta (TGF-β) signaling acts as the main factor in EMT. We investigate the correlation between high CD44 and TGF-β1 during EMT in HCC cell lines.

Methods: We determined the expression of CD44 by FACS and expression of TGF-β1 from the cell supernatant by ELISA. To investigate synergy effect of CD44 and TGF-β1, we induced EMT by TGF-β1 treatment. Also, we inhibited EMT by shCD44 and TGF-β1 inhibitors. Morphological changes were evaluated using microscopy and expression of EMT-related proteins detected by western blot. Also, EMT characteristics analyzed with sphere formation and migration assay.

Results: At the FACS analysis, the CD44 was highly expressed in SNU-354 and SNU-368 cell lines. TGF-β1 was only expressed in SNU-368 but not in SNU-354. SNU-368 CD44+ cells show EMT through up-regulation of AKT/GSK3β/β-catenin pathway. By comparison, SNU-354 CD44+ cells increased expression of N-cadherin but did not decrease the expression of E-cadherin, and then AKT/GSK3β pathway showed down-regulation. But, TGF-β1-treated SNU-354 cells exhibited morphological changes and accompanied by loss of E-cadherin and gain of N-cadherin with increased AKT/GSK3β/β-catenin. Also, TGF-β1-treated SNU-354 cells enhanced sphere formation and migration. On the other hand, TGF-β1-inhibited SNU-368 cells showed reduced N-cadherin and AKT/GSK3β/β-catenin. Also, TGF-β1 inhibition decreased sphere formation and migration. Moreover, the treatment with both shCD44 and TGF-β1-inhibitors reduced N-cadherin and AKT/β-catenin pathway and decreased migration in SNU-368 cells.

Conclusions: TGF-β1 increased the expression of EMT-related proteins with CD44 in SNU-354 cells. TGF-β inhibitors showed reversed EMT in SNU-368. In addition, co-expression of TGF-β1 and CD44 were needed for tumor metastasis because it significantly increased sphere formation and migration.

Keywords: CD44, EMT, TGF-β, HCC

PO - 054

Integrative Transcriptome and Metabolome Analysis of Hepatic Cancer Stem Cells

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Background: Liver cancer stem cells (LCSCs) are known to be responsible for cancer recurrence, metastasis and resistance to radiation and chemotherapy. Hence, understanding mechanisms of their resistance to several cancer treatments are critical in combating cancers. In an attempt to metabolic characterization by which CD133 expressing LCSCs mediate tumor formation and growth, metabolic pathway analysis was employed to compare metabolic changes between CD133+ and CD133-isolated from the HCC cells.

Methods: CD133(+) and CD133(-) Huh-7 cell were isolated by FACS. Transcriptomic profiles of CD133-expressing LCSCs and exo-metabolic profiles of 60 cancer cell lines were integrated with a human generic

metabolic model, Recon 2, to generate CD133(+)/(-) specific liver cancer metabolic models; these two models were employed to simulate their metabolic states.

Results: Metabolome analyses were conducted for both CD133(+) and CD133(-) Huh-7 cells in order to directly observe global metabolic changes through quantification of intracellular metabolites in these two types of LCSCs. In this study, we show that the intracellular ATP concentration was 42% higher in the metabolic model of the CD133(+) cells, compared to the CD133(-) cells. Furthermore, we have demonstrated that the increased expression of c-Myc in the metabolic model of the CD133(+) cells induced cell proliferation, glycolysis and glutaminolysis. c-Myc expression in CD133(+) cells induced fatty acid oxidation and mitochondrial biogenesis genes. Our data suggest that c-Myc expression in CD133-expressing LCSCs regulates glucose metabolism and mitochondrial biogenesis and is an important regulator of energy metabolism in the liver cancer in response to pathologic stress.

Conclusions: Integrative systems analysis involving constraint-based modeling and simulation was conducted to better understand metabolic characteristics of LCSCs and potential cues for their anticancer treatment resistances. In conclusion, the prediction results from these integrative systems metabolic analysis conducted herein will further contribute to elucidating metabolic pathway of liver cancer cell.

Keywords: Cancer stem cells, CD133, Metabolomics

PO - 055

Differential Hepatocarcinogenic Potentials between KRAS Splicing Variants

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Aims: In humans, three RAS genes encode four RAS proteins with a high degree of sequence homology: HRAS, NRAS, KRAS4A and KRAS4B, with the latter two resulting from alternative splicing of exon 4 of the KRAS gene. Activation of RAS signaling pathways is considered a key oncogenic event in human carcinogenesis. One unresolved question is whether there are differential oncogenic potentials among activated RAS isoforms.

Methods: Hydrodynamic transfection was performed with transposons expressing short hairpin RNA down-regulating p53 and each of activated RAS isoforms, and livers were harvested at 23 days after gene delivery to investigate the presence of tumors. Also, survivals of mice expressing different RAS isoforms were compared following hydrodynamic transfection.

Results: No differences were found in hepatocarcinogenic potentials among RAS isoforms as determined by both gross examination of livers and liver weight per body weight ratios (LW/BW) of mice expressing HRASQ61L, KRAS4BG12V, and HRASQ61L, respectively. However, tumorigenic potentials were significantly different between KRAS splicing variants. The LW/BW ratio in KRAS4AG12V mice was significantly lower than that in KRAS4BG12V group ($p < 0.001$) and KRAS4AG12V mice lived significantly longer than KRRAS4BG12V mice ($p < 0.0001$). Immunoblotting revealed that tumors from KRAS4AG12V mice had an elevated expression of p16INK4A compared with KRAS4BG12V tumors. Co-expression of p16INK4A with KRAS4BG12V significantly reduced tumor growth, suggesting that the up-regulation of p16INK4A by KRAS4AG12V likely retarded tumor development driven by KRAS4AG12V.

Conclusions: Oncogenic potentials differed significantly between the two KRAS splicing variants; KRAS4B being more tumorigenic than KRAS4A in the liver. Thus, it is presumed that when an activating mutation arises in KRAS, KRAS4B will predominantly lead the tumorigenic processes.

Keywords: Liver, Cancer, Kras

HCC, Clinical

PO - 056

Missing Cases in Diagnosis of HCC 2 cm or More Sizes

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Aims: The aim of this study was to analysis the cause of missing cases in diagnosis HCC 2cm or more sizes in Soonchunhyang University College of Medicine Cheonan Hospital about 10 years.

Methods: Between March 2006 and February 2014, 111 patients conducted HCC surveillance over 1 year among 726 patients diagnosed HCC by CT or MRI. We analysis retrospectively ultrasonographic finding of missing cases in diagnosis HCC 2cm or more sizes. We define "missing case" in the case of ultrasound performed two or more times within 1 year and diagnosis HCC 2cm or more sizes by CT or MRI after ultrasound.

Results: The total missing rate was 23.4% (26/111) in HCC surveillance, respectively. Missing case was 4 patients in chronic hepatitis B group (12 cases) and 22 patients in liver cirrhosis group (92 cases) (33.3% vs. 23.9%, p=0.593). Missing case was 12 patients in surveillance by one operator group (71 cases) and 14 patients in surveillance by multi operator group (40 cases) (16.9% vs. 35%, p=0.094). The total missing rate was 36% (40/111) based on more than 1cm, 23% (26/111) based on more than 2cm, 10% (11/111) based on more than 3cm. Missing rate was 33.8% (24/71) based on more than 1cm, 16% (12/71) based on more than 2cm, 4.2% (3/71) based on more than 3cm in surveillance by one operator group. Missing rate was 40% (16/40) based on more than 1cm, 35% (14/40) based on more than 2cm, 20% (8/40) based on more than 3cm in surveillance by multi operator group.

Conclusions: Ultrasonography is important test method to diagnosis and surveillance for HCC. But it affected by the ability of the operator, characteristics of HCC, size, location. To diagnosis small sized HCC,

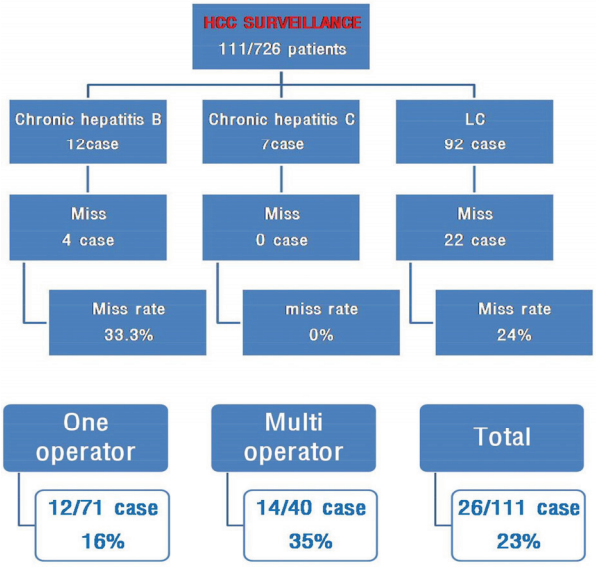

Figure1.

Size	Missing rate
> 1cm	36% (40/111)
> 2cm	23% (26/111)
> 3cm	10% (11/111)

One operator

Size	Missing rate
>1cm	33.8%(24/71)
>2cm	16%(12/71)
>3cm	4.2%(3/71)

Multi operator

Size	Missing rate
>1cm	40%(16/40)
>2cm	35%(14/40)
>3cm	20%(8/40)

Figure2.

The cause of missing diagnosis in less than 2cm HCC

Factor		Missing case
Echogenecity	Isoecho	5
Location	S7/8	4
	S2/3	3
	S4	2
	S6	2
	S1	1
Total		12/71 Patients

Figure3.

missing rate was lower in surveillance by one operator which know patient's clinical findings and examination results. In surveillance by one operator, missing cases were "blind spot" (dome, S7,8), isoechoic lesion, diffuse and infiltrative lesion. But all cases were confirmed by repeated ultrasonography after diagnosis by CT or MRI.

Keywords: Hepatocellular carcinoma, Ultrasonography, Surveillance

PO - 057

Development of Risk Prediction Model for Hepatocellular Carcinoma Progression of Indeterminate Nodules in Hepatitis B Virus-related Cirrhotic Liver

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Aims: This study was performed to evaluate long-term outcome of indeterminate nodules detected on cirrhotic liver and to develop risk prediction model for hepatocellular carcinoma (HCC) progression of indeterminate nodules on hepatitis B virus (HBV)-related cirrhotic liver.

Methods: Indeterminate nodules up to 2 cm with uncertain malignant potential detected on cirrhotic liver during HCC surveillance were analyzed retrospectively. HCC risk prediction model of indeterminate nodules in HBV-related cirrhotic liver was deduced based on result of Cox regression analysis.

Results: A total of 494 indeterminate nodules were included. Independent risk factors of HCC progression were old age, arterial enhancement, large nodule size, low serum albumin level, high serum alpha-fetoprotein (AFP) level, and prior HCC history in all included subjects. In subjects with chronic hepatitis B, old age (year; HR=1.06; P<0.001), arterial enhancement (HR=2.62; P=0.005), large nodule size (>1cm; HR=7.34; P<0.001), low serum albumin level (≤3.5g/dL; HR=3.57; P=0.001), high serum AFP level (≥100ng/mL; HR=6.04; P=0.006), prior HCC history (HR=4.24; P=0.001), and baseline HBeAg positivity (HR=2.31; P=0.007) were associated with HCC progression. We developed a simple risk prediction model using these risk factors and identified patients at low, intermediate, and high risk for HCC; 5-year cumulative incidences were 1%, 14.5%, and 63.1%, respectively. The developed risk score model showed good performance with area under the curve at 0.886 at 3 years, and 0.920 at 5 years in leave-one-out cross-validation.

Conclusions: We developed useful and accurate risk score model for predicting HCC progression of indeterminate nodules detected on HBV-related cirrhotic liver.

Keywords: Hepatocellular carcinoma, Indeterminate nodule, Risk score, Liver cirrhosis

PO - 058

Need for Subclassification of BCLC-C Stage Hepatocellular Carcinoma and Treatment Strategies

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Aims: Staging system of Barcelona Clinic Liver Cancer (BCLC) of hep-

atocellular carcinoma (HCC) is a very heterogeneous in terms of tumor size, tumor number, liver function and treatment option. However, Sorafenib is the only recommended treatment option according to the Barcelona Clinic Liver Cancer (BCLC) staging. Therefore, sub-classification of this heterogeneous patient population and indication of treatment strategy according to its substage is an extremely important issue to address.

Methods: One hundred and fifty six consecutive HCC patients with BCLC-C stage were retrospectively analyzed from July 2007 to December 2015. Baseline patients and tumor characteristics, therapy and overall survival were analyzed.

Results: The patients, predominantly men (76.9%), had a mean age of 70.6 years. Mean time of follow-up was 524 days (0-2996 days). Main etiology of liver disease was hepatitis B (51.9%), followed hepatitis C (14.4%). Median Child-Pugh scores was 5.8, and were classified as Child A/B/C in 80/17.5/2.5%. 156 patients with stage BCLC-C were classified as mUICC stage I/II/III/IVA/IVB in 1.9/15.4/50/29.5/3.2%, and were classified as AJCC TNM stage I/II/IIIA/IIIB/IIIC/IVA/IVB in 1.9/25.6/35.3/32.7/1.9/1.9/0.6%. First-line treatment method was classified as supportive care/resection/radiofrequency ablation (RFA)/transarterial chemoembolization (TACE)/TACE+RT/hepatic arterial chemoinfusion (HAIC)/Sorafenib/radiation therapy(RT)/sorafenib+RT/follow up loss in 12.5/11.3/0.6/59.4/1.9/1.3/0.6/0.6/8.8%.

Conclusions: Further subclassifications of the BCLC-C HCC patients are warranted to assess a finer prognostic tuning and more appropriate treatment allocation.

Keywords: BCLC staging, Hepatocellular carcinoma

PO - 059

Substaging of Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma by Tumor Size, Major Portal Vein Invasion, Distant Metastasis and Liver Function

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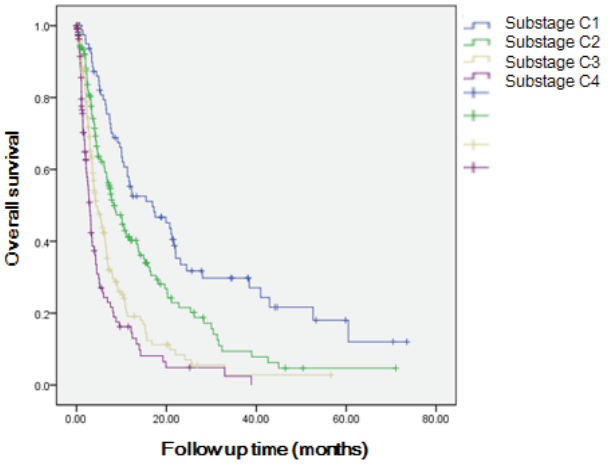
Aims: The hepatocellular carcinoma (HCC) with Barcelona Clinic Liver Cancer (BCLC) stage C encompasses a wide range of disease with various prognosis. We aimed to sub-stage the BCLC stage C for prediction of patient prognosis.

Methods: From January 2004 to December 2012, total 564 patients with newly diagnosed HCC BCLC stage C of the three tertiary hospitals affiliated with Korea University were analyzed retrospectively. The variables affecting overall survival (OS) were analyzed and the sub-staging was done.

Results: The mean follow up duration was 8.73 months [standard deviation (SD) ± 12.36]. Tumor factors such as size more than 10cm (HR 1.77, p<0.001), major portal vein invasion (type III portal vein invasion, HR 1.37, p=0.005), and distant metastasis (HR 1.43, p=004)



as well as Child-Pugh grade (HR 1.76, p<0.001) were proved to be independently associated with OS by multivariate analysis. Patients with BCLC stage C were sub-classified according to number of tumor factors which had the highest hazard ratios in multivariate analysis. Subsequently, four substaging system was made according to combination of tumor subclass and underlying liver function (compensated vs. decompensated). Substage C1 (n=83), substage C2 (n=174), substage C3 (n=189) and substage C4 (n=118) had median OS of 16.90 (95% CI 8.30-25.5), 8.27 (95% CI 5.98-10.6), 4.33 (95% CI 3.09-5.58) and 2.90 (95% CI 2.30-3.50) months, respectively (p<0.050 by log-rank test). The Bayesian information criterion (BIC) was 3951 for our BCLC substaging method and 3983 for Hongkong liver cancer substaging system (HKLC). Harrell's concordance index was 0.645 for BCLC substaging method and 0.624 for HKLC.

Conclusions: Substaging of BCLC stage C by tumor size, major portal invasion, distant metastasis and underlying liver function might be useful for discriminating patient prognosis. And our BCLC substaging system performs better than for HKLC in predicting overall survival.

Keywords: Hepatocellular carcinoma, BCLC, Stage

PO - 060

Sub-classification of Advanced Stage Hepatocellular Carcinoma based on a Real-life Cohort

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Aims: Advanced Hepatocellular carcinoma (HCC) embraces various clinical conditions: major vessel invasion, extrahepatic metastasis, and poor performance status. The aim of this study was to establish a prognostic scoring system using independent factors and to propose sub-classification of Barcelona-Clinic Liver Cancer (BCLC) stage C.

Methods: This retrospective study included consecutive patients who received sorafenib for BCLC stage C HCC at a single tertiary hospital in Korea. Factors affecting overall survival were analyzed. Cox proportional hazard model was used to develop a point score system, and

Table 1. Point scoring system

	Value	Points
Child-Pugh score	5-6	0
	7-9	7
Log(AFP)	0-3	0
	3-6	3
	6-9	6
	9-	10
Tumor type	Nodular	0
	Diffuse or infiltrative	5
Portal vein invasion	Absent	0
	Present	1
Extrahepatic metastasis	Absent	0
	Present	1
Total points		24

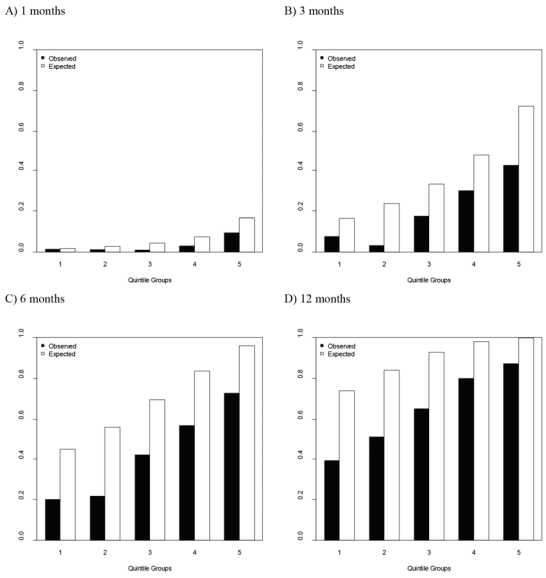

Figure 1. Calibration function of developed scoring system

internal validation was performed by 5-fold cross-validation. The performance of model to predict risk was assessed by area under the curve (AUC) and Hosmer-Lemeshow test.

Results: Among 756 patients who received sorafenib for HCC between 2008 and 2014, 612 (81.0 %) were classified as BCLC stage C and included in this study. Mean age of the patients were 60.3±10.7 and 84.2% were male. The patients were further classified into strata depending on their performance status (ECOG 0 or 1). Five independent prognostic factors (Child-Pugh score, alpha fetoprotein, tumor type, extrahepatic metastasis, and portal vein invasion) were identified and used in the prognostic scoring system. The scoring system gave from one to ten points for the presence each factor, resulting in a total score ranging from 0 to 24 (Table 1). This scoring system showed good discrimination (area under time-dependent ROC curve [AUC]=0.734-0.818) and calibration functions. (Figure 1) Cases were analyzed in the three risk groups according to the total score. In internal validation, AUC was similarly maintained (0.734 at month 12).

Conclusions: The result of heterogeneity of patients with BCLC stage C HCC requires sub-classification of advanced HCC. The prognostic scoring system using five independent factors is useful in predicting the survival of patients with BCLC stage C HCC.

Keywords: Hepatocellular carcinom, Scoring system, BCLC stage C

PO - 061

Effects of Endoscopic Variceal Ligation for the Esophageal Varix in Patients with Advanced Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis

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Aims: The outcomes of endoscopic variceal ligation (EVL) treatment of esophageal varices in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombus (PVTT) are unclear. We evaluated the short term (7-, 15-, 30-day) outcomes of emergency and prophylactic esophageal variceal band ligation (EVL) in HCC patients with PVTT.

Methods: From 2010 to 2012, 424 sessions of EVL were conducted in 242 HCC patients with esophageal varices. Clinical findings and outcomes were reviewed retrospectively. We assessed the bleeding-free and overall survival, and related prognostic factors were analyzed using the Kaplan-Meier method and a Cox proportional hazard model.

Results: All EVL sessions were conducted in patients with liver function Child-Pugh class A (159 sessions, 37.5%), class B (220 sessions, 51.9%), class C (45 sessions, 10.6%), and in modified UICC stage I/II (138 sessions, 32.5%), stage III/IV (93 sessions, 21.9%). Ninety-three (21.9%) sessions were conducted in the state of complete remission of HCC. Total 172 sessions of EVL were conducted in patients with PVTT; 115 (66.9%) sessions in patients with PVTT at the main portal trunk (Vp4) or first-order branch of the portal vein (Vp3). Major PVTT (Vp4 or Vp3) was predictive of esophageal variceal bleeding (hazard ratio 8.14, p<.0001). The 7-, 15-, 30-day bleeding-free survival rates of patients with major PVTT were 91.2%, 75.0%, 56.9% and they are significantly lower than that of patients without PVTT (98.0%, 95.6%, 92.0%, p<.0001, respectively).

Conclusions: After successful hemostasis with EVL, the bleeding-free survival rate was significantly lower in patients with major PVTT in comparison to patients without major PVTT. Non-invasive treatment may be first considered for esophageal varix in advanced HCC patients with main PVTT.

Keywords: Esophageal variceal ligation, Hepatocellular carcinoma, Portal vein tumor thrombosis

HCC, Clinical

PO - 062

Sarcopenia as a Predictor of Survival and an Objective Measure of Performance Status in Hepatocellular Carcinoma

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Aims: The prognostic impact of sarcopenia has not been clearly demonstrated in patients newly diagnosed with hepatocellular carcinoma (HCC), especially those without symptoms.
Methods: Area of skeletal muscle and abdominal fat were measured at L3 level of computed tomography scan in 132 patients newly diagnosed with HCC between Jan 2007 to Jun 2011. Sarcopenia was defined as L3 skeletal muscle index of ≤ 52.4 cm/m2 for male and ≤ 38.5 cm/m2 for female. Baseline data were analyzed to determine the effect of sarcopenia on overall survival (OS) using the univariate and Cox multivariate analyses in overall and propensity-score matched cohorts. The impact of sarcopenia in asymptomatic vs. symptomatic patients was subsequently evaluated.
Results: Sarcopenic patients (32 out of 132) were older (65.3 vs. 57.0 years old) and had lower body mass index (21.0 vs. 24.0 kg/m2), total fat (55.7 vs. 68.0 cm2/m2), and subcutaneous fat (21.9 vs. 29.2 cm2/m2) area. The presence of sarcopenia dichotomized patients with regard to OS (median 41.2 vs. 13.8 months, P=0.001). Multivariate analysis found that sarcopenia (hazard ratio [HR], 2.15, P=0.008), alpha-fetoprotein (HR, 2.79, P=0.004), Child-Pugh stage (HR, 2.38, P=0.017), infiltrative tumor (HR, 2.29, P=0.021), and BCLC stage (P<0.001) were predictive of OS. In a propensity score-matched cohort, sarcopenia (HR, 5.50, P=0.027) was the only predictive factor. In particular, asymptomatic patients with sarcopenia had a poor OS than patients without sarcopenia (median 69.6 vs. 22.2 months, P<0.001), while no significant difference in symptomatic patients (median 17.2 vs. 9.7 months, P=0.26). Subdividing asymptomatic patients of BCLC A and B stages according to sarcopenia status improved the predictive ability of staging system (c-index, 0.87 vs. 0.67, P<0.001).
Conclusions: Sarcopenia is an independent prognostic factor in patients newly diagnosed with HCC, especially those without symptoms. Subdividing BCLC A and B stages according to sarcopenia status showed a better stratification.
Keywords: Sarcopenia, Hepatocellular carcinoma, Survival, Performance status

PO - 063

Prognostic Values of Inflammation and Immune-based Scores in Patients with Hepatocellular Carcinoma Who Undergo Transarterial Chemoembolization

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Aims: We investigated whether baseline inflammation and immune-based scores predict prognosis of hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE).
Methods: A total of 615 consecutive patients with HCC who had undergone TACE as initial treatment were included from a prospective cohort. The systemic immune inflammation index (SII) defined as (platelet count × neutrophil)/lymphocyte, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) were analyzed with regard to their associations with disease progression and survival.
Results: All of the tested inflammation/immune-based scores were significantly associated with overall survival in the univariate analysis. In the multivariate analyses, SII levels were independent risk factors for poorer survival together with BCLC stage, serum AFP levels, maximum tumor size, and Child-Pugh score. The hazard ratio of death for each increase in SII level was 3.483 (95% confidence interval, 1.971-6.156; p<0.001). Furthermore, SII significantly improved discrimination function of BCLC stage in predicting overall survival.
Conclusions: High baseline SII independently correlated with poorer OS in patients with HCC who underwent TACE.
Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Systemic immune-inflammation index, Prognosis

PO - 064

Plasma MicoRNA-21, 26a, and 29a as a Predictive Marker for Treatment Response Following Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

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Aims: We investigated the association between plasma microRNA-21, 26a, and 29a levels and the treatment outcomes following transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients.
Methods: We included 198 HCC patients treated with TACE in the study; TACE refractoriness and liver transplantation (LT)-free survival were evaluated during follow-up. Pretreatment plasma microRNA-21, 26a, and 29a levels were assessed using quantitative real time polymerase chain reaction. Relative quantification of miR expression (fold change) was determined using the 2(-ΔΔCt) method.
Results: During the mean follow-up of 22.3 (range, 0.7-79) months, 118 (59.6%) patients exhibited TACE refractoriness. Multivariate analyses showed that tumor size (hazard ratio [HR], 2.43; 95% confidence interval [CI], 1.27-4.67; P = 0.007), macrovascular invasion (HR, 2.18; 95% CI, 1.28-3.72; P = 0.004), and high pretreatment alpha-fetoprotein level (>400 ng/ml; HR, 1.88: 95% CI (1.22-2.90; P = 0.004) can independently predict overall TACE refractoriness. Combination of microRNAs expression (microRNA-21 ≥2.5, microRNA-26a ≥1.5, and microRNA-29a <0.4) was associated with early TACE refractoriness (within 1 year; HR, 2.32; 95% CI, 1.08-4.99; P = 0.031), together with tumor size (HR, 4.62; 95% CI, 1.50-14.21; P = 0.008), and vascular invasion (HR, 3.80; 95% CI, 1.19-12.20; P = 0.025). MicroRNA-21, microRNA-26a, and microRNA-29a levels were not sig-

nificantly associated with LT-free survival.
Conclusions: Combination of plasma microRNA-21, 26a, and 29a expression was associated with early TACE refractoriness in HCC patients treated with TACE.
Keywords: Chemoembolization, Hepatocellular carcinom, MicroRNA-21, MicroRNA-26a, MicroRNA-29a, Survival, Treatment failure

PO - 065

EpCAM as a Predictive Marker of Tumor Recurrence and Survival in Patient with Hepatocellular Carcinoma after Surgical Resection

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Aims: Epithelial cell adhesion molecule (EpCAM) is a biomarker for hepatic stem cell because it is expressed in hepatic progenitor cell and fetal hepatoblast. We evaluated the expression of stemness-related markers as a prognostic marker of tumor recurrence and survival in patient with hepatocellular carcinoma (HCC) underwent surgical resection.
Methods: We enrolled 204 HCC patients who had performed surgical resection between Jan 2011 and Dec 2014. Protein expression of EpCAM, alpha-fetoprotein (AFP), cytokeratin 19 (CK19), cytokeratin 7 (CK7) and glypican-3 were examined using immunohistochemical stain in resected specimens. The prognostic significance of EpCAM and other markers was analyzed using Kaplan-Meier and Cox regression models.
Results: Expression of EpCAM, AFP, CK19, CK7 and glypican-3 were positive in 46.1% (88 out of 191), 47.8% (88 out of 184), 33.3% (31 out of 93), 51.5% (68 out of 132) and 87.5% (162 out of 185), respectively. Univariate Cox regression analysis showed that Edmondson grade (I, II vs III, IV), microvessel invasion, portal vein invasion, hepatic vein invasion, intrahepatic metastasis and EpCAM expression were associated with tumor recurrence (P=0.014) and disease-free survival (DFS)(P=0.019). A Kaplan-Meier survival analysis showed that patients with EpCAM positive staining had significantly higher tumor recurrence (P=0.0123) and lower DFS (P=0.0179) than patients with EpCAM negative staining. Other markers (AFP, CK19, CK7, glypican-3) were not associated with tumor recurrence or survival. In subgroups analysis with hepatitis B virus-related HCC (n=168), EpCAM positivity was also associated with tumor recurrence (P=0.0277) and DFS (P=0.0189) in Kaplan-Meier analysis.
Conclusions: EpCAM expression might be a poor prognostic maker of tumor recurrence and survival in patients with HCC after surgical resection.
Keywords: EpCAM, Predictive marker, Hepatocellular carcinoma

PO - 066

The Comparison Study between Contrast-enhanced Ultrasonography and Dynamic Contrast-enhanced Computed Tomography to Assess the Response of Transarterial Chemoembolization for Hepatocellular Carcinoma: A Prospective Pilot Study

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Aims: Multidetector computed tomography (MDCT) is commonly used to evaluate therapeutic effect of posttreatment response of transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). However, dense lipiodol uptakes after TACE can lead to misinterpretation of detecting viable tumor in MDCT. We prospectively compared contrast-enhanced ultrasonography (CEUS) and MDCT to evaluate the residual tumor of HCC after treatment with TACE by using hepatic arteriography as a golden standard.
Methods: MDCT and liver dynamic magnetic resonance imaging (MRI) were obtained from nine patients at baseline to diagnose HCC. We investigated residual tumor using CEUS and MDCT four weeks after TACE. All patients received hepatic arteriography a week after CEUS and MDCT to confirm viable tumor after TACE.
Results: All nine patients (six males and three females, mean age 59±8.9 years-old range of 40-69 years-old) had Child class A. One patient had modified UICC stage of I, six patients had stage II, and two patients had stage IVA. Five of the nine patients showed CEUS positivity and four patients showed MDCT positivity four weeks after TACE. One patient with negative CEUS findings at the fourth week had positive results on the fifth week's hepatic arteriography. Two patients with negative MDCT findings at the fourth week were confirmed to have residual HCC lesion at the fifth week's hepatic arteriography. Kappa statistics revealed excellent agreement between CEUS and hepatic arteriography (k=0.791, p=0.025) and substantial agreement between MDCT and hepatic arteriography (k=0.632, p=0.074).
Conclusions: In the assessment of the treatment response to TACE, CEUS at the fourth week showed excellent results for diagnosis of viable HCC. We suggest CEUS can be an useful alternative diagnostic tool considering early additional treatment with TACE.
Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Contrast-enhanced ultrasonography, Multidetector computed tomography

PO - 067

Clinical Significance of the Peritumoral Decreased Uptake Area on Hepatobiliary Phase of Gadoxetic Acid-enhanced MRI in Hepatocellular Carcinoma

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Aims: Vascular invasion is the most important predictive factor of tumor recurrence after resection in hepatocellular carcinoma (HCC). Recently, it has been suggested that the peritumoral decreased uptake area (PDUA) on hepatobiliary phase of gadoxetic acid-enhanced MRI could be shown in cases of the impaired hepatocyte function induced by decreased portal flow, and was associated with vascular invasion in HCC. The aims of our study were to clarify the clinicopathological characteristics of PDUA on hepatobiliary phase and to elucidate the predictability of the PDUA on tumor recurrence after resection.

Methods: We retrospectively analyzed the clinicopathological and radiological data from 194 consecutive HCC patients who underwent preoperative gadoxetic acid-enhanced MRI and surgical resection between January 2008 and January 2016. The presence of a faint and hypointense area around the tumor in the hepatobiliary phase was defined as PDUA.

Results: Of 194 HCCs, PDUA on hepatobiliary phase was observed in 25 cases (12.9%). Of 42 HCCs with microvascular invasion, PDUA was observed in 16 cases (38.1%) and of 16 HCCs with macrovascular invasion, PDUA was observed in 8 cases (50.0%). In multivariate analysis, tumor size (>5 cm) and microvascular invasion were significantly associated with PDUA. After a median follow-up period of 17.5 months, 17 of the 25 patients with PDUA (68.0%) suffered from tumor recurrence. The recurrent-free survival in group with PDUA after resection by Kaplan-Meier method with the log-rank test was significantly worse than that in group without PDUA (P=0.003). In addition, multivariate survival analysis using Cox's regression identified that PDUA (HR =4.2; 95% CI 1.8-9.7; P=0.001) was an independent risk factor for recurrence after resection of HCCs less than 5 cm.

Conclusions: PDUA on hepatobiliary phase of gadoxetic acid-enhanced MRI could be a useful preoperative predictor of microvascular invasion and prognosis factor after surgical resection in HCC.

Keywords: Hepatocellular carcinoma, Peritumoral decreased uptake area, Hepatobiliary phase, Gadoxetic acid-enhanced MRI

HCC, Clinical

PO - 068

Doubling Time of Serum Tumor Marker in HCC Patients Predicts Recurrence after Curative Treatment

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Aims: Alpha-fetoprotein (AFP) and protein-induced vitamin K absence (PIVKA-II) have been used as a marker for hepatocellular carcinoma (HCC). We aimed to investigate the correlation of doubling time (DT) of tumor markers (AFP, PIVKA-II) after curative treatment with recurrence of HCC.

Methods: Between January 2005 and December 2013, total of 451 patients were enrolled. After excluding the patient with loss to follow-up, tumor remnant and absence of repeated tumor marker, 213 patients who received curative treatment were analyzed (Liver transplantation, surgical resection, radiofrequency ablation, percutaneous ethanol injection). Serum AFP and PIVKA II levels before and after the curative treatment were collected and used for analysis. Tumor marker DT was calculated as DT=t log 2/(log (marker 2nd)-log (marker 1st)) where t was the time interval between from nadir level after treatment to level at recurrence or 2 years later after treatment.

Results: Mean age was 56 years. HBV infection was the most common etiology of HCC (78.4%), and most of the patients were in BCLC stage 0 and A (77.9%). During the follow up, 127 of 213 patients (59.6%) were recurred. Median DT of AFP and PIVKA-II was 20months and 18.7months. In comparing the HCC patients with or without early recurrence, DT was significantly lower in the early recurrence group (AFP and PIVKA II: 10.4 vs 26.78 months; P<0.001 and 8.75 vs 24.67 months; P<0.001, respectively). In univariate analysis, BCLC stage, tumor size, PIVKA-II level at diagnosis, AFP DT and PIVKA-II DT were significantly related to recurrence rate. In multivariate analysis, AFP DT and PIVKA-II DT and BCLC stage at diagnosis were only independent predictor of recurrence after curative treatment on HCC.

Conclusions: In HCC patients with curative treatment, the DT of AFP and PIVKA-II from nadir level after the treatment is useful tools to predict early recurrence.

Keywords: Doubling time, AFP, PIVKA, Hepatocellular carcinoma

PO - 069

Assessment of Risk for Recurrence of Hepatocellular Carcinoma: An Extended Surveillance Interval 1 Year after Curative Treatment

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Aims: The guidelines recommend surveillance for hepatocellular carcinoma recurrence be performed 3-monthly during 1 year after curative treatment, and 6-monthly thereafter in all patients. This strategy did not reflect individual risk based on patients' tumor biology. We aimed to identify patients who can extend surveillance intervals 1 year after

treatments.

Methods: We retrospectively analyzed 1,490 patients treated with hepatectomy/radiofrequency ablation in the Barcelona Clinic Liver Cancer stage 0/A and well-preserved liver function. In patients under 3-monthly surveillance in total periods, a new model for survival was developed using multivariable analysis: the derivation (n=682)/validation set (n=341). Survival rates in low-risk patients by the new model were compared according to surveillance intervals 1 year after treatments: 3-monthly vs. 6-monthly (n=467) after propensity score matching and lead time bias correction.

Results: Albumin levels, MELD score, tumor size, alpha-fetoprotein levels, and 1-year recurrence were independent factors for survival: odds ratios (OR) of 0.33, 1.12, 1.06, 1.09, and 6.99 respectively (all P<0.01). One-year recurrence showed significantly higher OR than other durations (1-2, 2-3, and >3 years, P<0.01). A new model showed AUROC of 0.81 (the derivation set) and 0.77 (the validation set). Survival rates in low-risk patients of the new model under 3-monthly surveillance 1 year after treatments were not superior to those under 6-monthly surveillance (P=0.958).

Conclusions: Surveillance interval 1 year after treatments in patients with favorable tumor biology can be extended to 6-monthly interval. Surveillance schedules can be optimized to reduce radio hazard and cost without compromising benefits in low-risk patients.

Keywords: Surveillance interval, Hepatocellular carcinoma, Curative treatments, Risk stratification

PO - 070

Does Transarterial Chemoembolization prior to Surgical Resection Improve Clinical Outcomes in Resectable Hepatocellular Carcinoma?

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Background: The efficacy of transarterial chemoembolization (TACE) performed prior to surgical resection inpatients with resectable hepatocelluar carcinoma (HCC) is still a matter of debate. This study aimed to assess the impact of preoperative TACE in patients withresectable HCC.

Methods: A total of 117consecutive HCC patients who received hepatectomy at the Incheon St. Mary's Hospitalbetween 2008 and 2015were enrolled.19 patients who eitherreceived more than 3 sessions of TACEs prior to resection were excluded. 98 patients underwent resection after conventional staging work up(non-TACE group) and 19 patients received a single or two sessions of TACEs before resection (TACE group).

Result: The median follow up period was 30.9 months (range, 6.5-52.9). According to the modified UICC stage, 28 (23.9%) patients were diagnosed as stage 1, 73 (62.4%) as stage 2, and 16 (13.7%) patients as stage 3.No difference was observed in terms of the age, Child-Pugh score, level ofalpha-fetoprotein, and tumor stage betweenthe two groups.In the TACE group, three new HCC lesionswhich were not identifiable with MRI were found in 3 patientson angiography and resected with the original lesion together.No difference was observed in the disease-free survival (DFS) and overall survival (OS)between the two groups with the mean DFS of 56.1 vs. 53.4 months (p=0.278) and mean OS of 73.9 vs. 60.2 months (p=0.358) in the TACE group and the non TACE group, respectively.

Conclusion:TACE performed prior to surgical resection does not enhance DFS or OS in the patients with resectable HCC.

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Resection, Survival

PO - 071

Prognosis of Early Stage Hepatocellular Carcinoma Showing Complete Response after First Transarterial Chemoembolization: A Role of Scheduled Second TACE

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Aims: Transarterial chemoembolization (TACE) is performed with curative intent in some patients with early stage hepatocellular carcinoma (HCC) in real clinical practice. As radiological complete response (CR) after TACE does not always match histological total necrosis, scheduled second TACE has been tried for early stage tumor with complete response after first TACE, which lacks sufficient supporting data.

Methods: A total of 178 patients with early stage HCC, defined by Barcelona Clinic Liver Cancer stage (BCLC) 0 or A, who were initially treated with TACE and showed CR by mRECIST criteria at one month follow-up computed tomography (CT) were analyzed. Among them, 90 patients received scheduled second TACE in absence of viable tumor at one month follow-up CT, while 88 patients were monitored without TACE until viable lesions are detected (on-demand approach).

Results: During a median 4.6 years of follow-up (range: 0.4 - 8.8 years), mortality was observed in 71 patients (39.9%), with a 5-year survival rate of 60.4%. Overall and local tumor recurrence was observed in 135 (75.8%) and 103 (57.9%) patients. The overall and local recurrence-free survival rate at 1 year was 44.4% and 56.2%. In multivariable model, treatment strategy (scheduled second TACE vs. on-demand) was independent factor associated with survival [hazard ratio (HR) (95% confidence interval (CI)): 0.56 (0.34-0.93), p = 0.025], along with underlying liver disease, Child-Pugh class, and BCLC stage. BCLC stage was more advanced for those who received scheduled second TACE. When stratified according to the BCLC stage, scheduled second TACE was associated with favorable overall survival rate (62.1% vs .39.1% at 5-years) and lower local recurrence rate (68.1% vs. 89.5% at 2-years) in BCLC stage A patients, but not in BCLC 0 patients.

Conclusions: Scheduled second TACE was associated with better survival and lower local recurrence rate for BCLC A stage tumor showing

CR after initial TACE . Scheduled second TACE strategy may play a significant role for this subset of early-stage HCC patients, which warrants further validations.

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Survival

PO - 072

Three-dimensional Conformal Radiotherapy for Portal Vein Tumor Thrombosis in Advanced Hepatocellular Carcinoma

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Aims: We sought to evaluate the clinical outcomes of 3-dimensional conformal radiation therapy (3D-CRT) for portal vein tumor thrombosis (PVTT) in patients with advanced hepatocellular carcinoma.

Methods: We retrospectively analyzed data on 99 patients who received 3D-CRT for PVTT alone between June 2002 and December 2015. Response was evaluated following the Response Evaluation Criteria in Solid Tumors.

Results: Twenty one patients (21.2%) had age over 65 years and forty patients (40.4%) had Child-Pugh class B. The Eastern Cooperative Oncology Group performance status was 2 in 23 patients (23.2%). Forty eight patients (48.5%) had main or bilateral PVTT. The median irradiation dose was 50 Gy (range, 10-60 Gy), the daily median dose was 2.172 Gy (range, 1.8-3 Gy) and median number of fraction was 25 (2-30). 70 (70.7%) patients treated with transarterial chemoembolization (TACE) followed by 3D-CRT and 29 patients were treated with 3D-CRT alone. PVTT response was complete response in 3 patients (3.1%), partial response in 36 (36.4%), stable disease in 35 (35.4%), and progressive disease in 17 (17.2%). In overall tumor response, complete response was 1 (1.0%), partial response was 22 (22.2%), stable disease was 23 (23.2%), and progressive disease was 46 (46.5%). PVTT response was significantly associated with number of radiation fraction (p=0.044). Overall objective tumor response was significantly associated with number of radiation fraction (p=0.040) and metastatic status (p=0.046). There were 5 cases of grade 3 liver function aggravation during or 1 months after radiotherapy. The 1-year and 2-year survival rate was 40.2% and 19.3%, respectively. Survival was significantly associated with overall tumor response (p=0.034), etiology (p=0.007) and number of radiation fraction (p=0.035).

Conclusions: Conformal radiotherapy with or without TACE for PVTT could be chosen as a palliative treatment modality in patients with unfavorable conditions (liver, patient, or tumor factors).

Keywords: Hepatocellular carcinoma, Portal vein tumor thrombosis, 3-dimensional conformal radiotherapy

PO - 073

Radiation Induced Liver Disease after Stereotactic Body Radiation Therapy for Small Hepatocellular Carcinoma : Risk Factor and Clinical Significance

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Aims: The aim of this study was to identify parameters that predict radiation induced liver disease (RILD) following stereotactic body radiotherapy (SBRT) in cirrhotic patients with small hepatocellular carcinoma (HCC).

Methods: We retrospectively reviewed 84 patients treated with SBRT for small (diameter <3 cm) HCC treated by SBRT between March 2011 and February 2015. RILD was defined as elevated liver transaminases more than five times the upper limit of normal or a worsening of Child-Pugh score by 2 within 3 months after SBRT. All patients were assessed at 1 month and every 3 months after SBRT.

Results: Median follow-up was 16.5 (2-56) months after SBRT. Seventeen (18.5%) of the 84 patients developed RILD after SBRT. Multivariate logistic regression analysis showed that Child-Pugh (CP) scores ($p < 0.01$) was significant parameter to predict RILD in cirrhotic patients. According to linear by linear association model, as CP score increases, the incidence rate of RILD ($P<0.01$) increases, and the recov-

Table 3. Multivariate analysis of parameters associated with risk of RILD

	Non Classic RILD		
Variables	OR	95% CI	P value
CTP score			
5	reference		
6	12.214	1.731 - 86.178	0.012
7	28.500	3.377 – 240.511	0.020
≥8	228.000	18.494 – 2821.928	<0.01*
PVT			
Yes/ No	2.465	0.406 – 14.959	0.327
Total liver volume	0.999	0.996 – 1.002	0.667

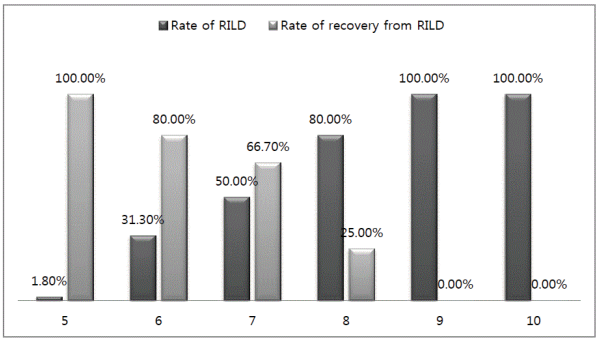

Fig 1 Rate of RILD and recovery rate from RILD
Linear by linear association model.

Figure 1. Rate of RILD and recovery rate RILD Linear by linear association model.

ery rate of RILD (P<0.01) shows a tendency to decrease. The incidence rate of RILD increases at CP score 6 remarkably, and the recovery rate of RILD seems to decrease significantly at CP score 8. In multivariate analysis, CP score 8 was independent prognostic factors of overall survival. (P<0.01)

Conclusions: CP score is important factor to predict RILD. The Incidence rate of RILD seems to increase, but does not recover at CP score above 8.

Keywords: Hepatocellular carcinoma, Stereotactic body radiation therapy, Radiation induced liver disease

HCC, Clinical

PO - 074

Clinical Outcomes of Patients with a Single Hepatocellular Carcinoma Less Than 5 cm Treated with Transarterial Chemoembolization

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Background: Transarterial chemoembolization (TACE) is an alternative treatment for small-sized single hepatocellular carcinoma (HCC) that are not eligible for surgery or ablation therapy. We aimed to investigate the clinical outcomes of patients with a single HCC less than 5cm treated with TACE.

Methods: From August 2003 to October 2014, 361 patients were treated with TACE as a first treatment. Among these, 74 patients had a single HCC less than 5cm. We analyzed complete response (CR) after TACE and predictive factors for overall survival (OS) in these patients.

Results: Sixty-five patients (87.8%) had liver cirrhosis (Child A/B/C, 40/23/2). Forty-five patients (58.1%) had modified UICC stage I, 30 patients (40.5%) had stage II, and one patient (1.4%) had stage III. Median tumor size was 1.9cm (range, 1.0-4.6cm). Median alphafetoprotein (AFP) was 9.1 ng/ml (range, 1.3-10268 ng/ml). Thirty nine patients (52.7%) achieved CR after TACE and seventeen patients (43.6%) recurred after CR (local recurrence/distant recurrence, 15/2). The 1-, 3-, 5-year OS rates were 86.2%, 65.4%, and 30.3%, respectively. Median OS was 30.6 months (95% CI, 24.5-36.7) for non-CR group and 78.1 months (95% CI, 44.1-112.2) for CR group (p=0.003). In multivariate analysis, CR (p=0.011), modified UICC stage I (p=0.043) were positive predictive factors, and ascites (p=0.011) was negative predictive factor for OS.

Conclusions: TACE is a valid treatment option in patients with a single HCC not suitable for curative treatment. CR, modified UICC stage, and ascites were predictive factors for OS.

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Response, Survival

PO - 075

Long Term Results of Combined Transarterial Chemoembolization with Radiofrequency Ablation in Hepatocellular Carcinoma of 2 to 5 cm in Diameter

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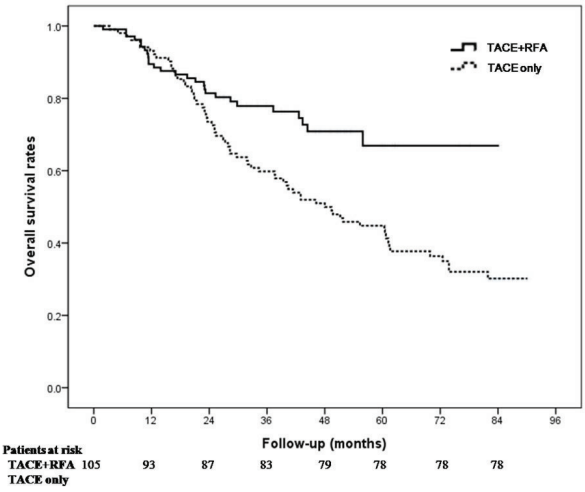
Aims: To evaluate the long term efficacy and safety of combined transarterial chemoembolization (TACE) with radiofrequency ablation (RFA) and transarterial chemoembolization(TACE) only in patients with hepatocellular carcinoma of 2 to 5 cm.

Methods: This was a retrospective case control study including 207 consecutive patients consisting of 105 patients who underwent combined TACE with RFA and 102 patients who underwent TACE only with long term follow up.

Results: The complete remission rate was significantly higher in the combination group (97.1%, 102/105) than in the TACE group (54.9%, 56/102) (p=0.000).The mean follow-up periods of the combination group and the TACE group were 49.3±16.9 months and 46.3±26.7 months. The TACE group (90.2%, 92/102) showed significantly higher tumoral recurrence or persistence than the combination group (59.0%, 62/105) during follow-up periods (p=0.000). The cumulative survival rates at 1, 2, 3, 4, and 5 years were 88.6, 82.9, 79.0, 75.2, and 74.3% in the combination group and 93.1, 73.5, 59.8, 50.0, and 45.1% in the TACE group. Independent factors associated with improved overall survival were the combination group, Child-Pugh class A, complete remission at 1 month, negative intrahepatic new tumors, and adverse event.

Conclusions: Complete local tumor control by combination of TACE with RFA could improve overall survival compared with TACE only



for long term follow up. The combination of TACE with RFA should be considered for achieving complete local tumor control before progression to advanced stage in patients with hepatocellular carcinoma (HCC) of 2 to 5 cm.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation, Transarterial chemoembolization

PO - 076

Transarterial Infusion of Epirubicin and Cisplatin Combined with Systemic Infusion of 5-FU for Advanced Hepatocellular Carcinoma Refractory to Conventional Transarterial Infusion with Doxorubicin

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Aims: Transcatheter arterial chemoembolization (TACE) has been recognized as an effective therapy for advanced hepatocellular carcinoma (HCC). However, there are a few limited options including sorefenib in case of tumor progression after TAC with single agent, doxorubicin (TAC-DOX). As a novel therapeutic strategy, the efficacy of transarterial infusion of epirubicin and cisplatin combined with systemic infusion of 5-fluorouracil (5FU) (TAC-ECF) in HCC patients with progression after TAC-DOX was investigated.

Methods: A total of 405 consecutive HCC patients who received TAC-DOX at the Catholic Medical Center between 2008 and 2015 were enrolled. Of these patients with the tumor progression after TACE-DOX (median 3 times, range 1~15 times), 34 patients who had treated with TAC-ECF were finally analyzed. TAC-ECF consisted of transarterial infusion of epirubicin (50 mg/m2) and cisplatin (60 mg/m2) combined with systemic infusion of 5-FU (200 mg/m2). Tumor response was evaluated by modified RECIST criteria and overall survival (OS), progression free survival (PFS) were checked.

Results: All patients presented with Eastern Co-operative Group performance status (ECOG) 0-2 and the Child-Pugh classification with A and B. The stage (modified UICC stage) of 34 patients was followed by stage 3 (n=5), 4A (n=15) and 4B (n=16). Median follow up period was 145 days (range, 40~635 days). The tumor response for TAC-ECF was complete resolution (CR) in 1 patients (2.9%), partial response (PR) in 2 patients (5.9%), stable disease (SD) in 14 patients (41.2%) and progression disease (PD) in 17 patients (50.0%). The median progression-free survival (PFS) during TAC-ECF was 105 days (95% CI 34.4-175.5). The overall survival was 152 days (95% CI 119.2-184.7). The overall survival rate in the objective response (CR, PR, and SD) group was also significantly higher than in the PD group (median 223 days vs. 119 days, P< 0.001).

Conclusions: TAC-ECF therapy achieved acceptable progression free survival in the patients who progressed after TAC-DOX. It also showed higher survival rate in the patients with objective response than the patients with progressive disease. Therefore, TAC-ECF may be considered as an effective treatment option for patients with advanced HCC refractory to TAC-DOX.

Keywords: Hepatocellular carcinoma, Transcatheter arterial chemoembolization, Doxorubicin, Epirubicin

PO - 077

Safety and Feasibility of Laparoscopic Major Hepatectomy (LMH) Post Portal Vein Embolization (PVE), A Case Series

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Purpose: PVE before a major hepatectomy is selectively indicated, the safety & feasibility of LMH is well established, however, LMH post PVE is fraught with technical challenges, this case series of 15 patients demonstrate its safety and feasibility.

Methods: Between May 2012 and September 2014, at Samsung Medical Center, 15 patients underwent LMH after PVE. Median age was 58 year old (32-79),13 males, 2 females, 10 cases of HCC-B, 2 CLM (colorectal liver metastasis), 1 CCC (cholangiocarcinoma), 2 HCC/CCC (combined hepatocellular and cholagiocarcinma), 12 had early stage (I & II), 1 stage IVa CCC, median tumor number was 1 (1-3), median tumor size was 5cm (1.8-8), median CTP (Child-Turcot-Pugh) score of 6 (5-6), median initial FLR volume ratio was 24.29% (16.8-28.81) (of SLV), median post-PVE FLR Volume ratio was 42.56% (33.72-46.92), with a median net increase of 71.30% (38.82-110.4), over a median interval of 21 days (14-42).

Results: 11 cases underwent LRHH (laparoscopic right hemihepatectomy), while 4 underwent LeRH (laparoscopic extended right hemihepatectomy),median operative time was 324 minutes (246-803), median EBL (estimated blood loss) was 100 ml (range 50-300 ml), no conversion to open, no intraoperative transfusion, 1 patient had a postoperative intraabdominal bleeding which responded to transfusion therapy, no reoperation, 1 incident of biliary leak & obstruction responded successfully to PTBD (percutaneous transhepatic biliary drainage) and ERBD (endoscopic retrograde biliary drainage), 1 incident of upper limb DVT (deep vein thrombosis), 1 incident of transient post-hepatectomy hepatic insufficiency followed by full recovery, 1 incident of SSI (surgical site infection) after a combined colectomy, median resectional margin 1cm (0.1-5), median LOS (length of stay) was 9 days (5-37), 1 mortality due to stroke on POD (postoperative day) 37.

Conclusion: LMH after PVE seems relatively safe and feasible with acceptable morbidity & mortality, and Glissonian pedicle is thick post PVE so we advise to avoid using a white cartridge and to opt for a tan cartridge for more secure staple line.

PO - 078

Can Sorafenib Increase Survival for Recurrent Hepatocellular Carcinoma after Liver Transplantation?

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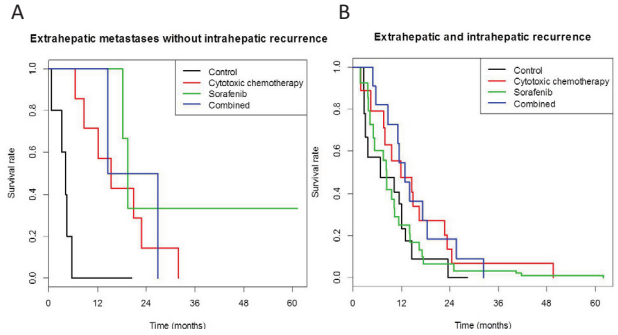

Figure 1. Survival after recurrence according to treatment
(A) Patients with extrahepatic metastases without intrahepatic recurrence
(B) Patients with extra/intrahepatic recurrence transplantation, Sorafenib, Efficacy

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Aims: The efficacy of sorafenib in post liver transplantation (LT) era has been rarely studied. The aim of this study was to evaluate the efficacy of sorafenib in patients with HCC recurrence after LT.
Methods: Consecutive patients who developed HCC recurrence after LT were included. Treatment outcome was investigated in terms of survival from recurrence or from untreatable presentation/progression (UP) by Cox regression analyses with event times left-truncated at the time of UP.
Results: Of a total of 90 patients, 45 received sorafenib treatment (31 sorafenib, 14 sorafenib and second line cytotoxic chemotherapy) and 45 received cytotoxic chemotherapy or best supportive care only (20 cytotoxic chemotherapy, 25 best supportive care). The baseline characteristics of two groups were well balanced, with treatment period related imbalances regarding mTOR-based immunosuppression and number of treatment after recurrence, significantly higher in the sorafenib group. Survival after recurrence was not significantly different between two groups. However, in patients who developed extrahepatic metastases without intrahepatic recurrence, those treated with sorafenib and/or systemic chemotherapy showed a better survival rate than those receiving best supportive care only (median survival from recurrence: 18.1 vs. 4.2 months, HR=0.18, P=0.003; median survival from UP: 19.4 vs. 4.5 months, HR=0.07, P=0.001). In the multivariate analysis, the only factor associated with survival after HCC recurrence was treatment with sorafenib and/or cytotoxic chemotherapy (HR=0.07; P=0.001). On the contrary, neither sorafenib nor cytotoxic chemotherapy demonstrated meaningful efficacy in patients who developed intrahepatic recurrence with/without extrahepatic metastases.
Conclusions: In patients with post-transplant HCC recurrence, sorafenib seems to be effective in extrahepatic metastatic tumor; however, it has limited efficacy in the treatment of intrahepatic recurrence.
Keywords: Hepatocellular carcinoma, Liver

HCC, Clinical

PO - 079

An Analysis for Survival Predictors for Patients with Hepatocellular Carcinoma Who Failed to Soraefnib Treatment

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Aims: Although sorafenib is the standard treatment of patients with advanced hepatocellular carcinoma (HCC), substantial patients experience failure of sorafenib therapy due to progression, adverse effect and clinical decompensation. We aimed to investigate the prognosis predictors and the role of 2nd-line systemic chemotherapy in patients with advanced HCC who failed by sorafenib therapy.
Methods: From 2007 to 2015, the medical records of 166 HCC patients who permanently discontinued sorafenib therapy with any cause were retrospectively reviewed. For further analysis of survival factors after sorafenib failure, we divided the 2nd-line treatment patients as systemic chemotherapy group, selected best supportive care (BSC) group consisted with favor general condition and liver function, and terminal supportive care group consisted with poor general condition and/or liver function.
Results: Mean age was 57.8 years and chronic hepatitis B (74.1%) was main attributable factor in development of HCC. After discontinuation of sorafenib, median overall survival (OS) was 2.8 (1.9-3.7) months. The survival in patients who discontinued sorafenib due to adverse effect, progression and poor clinical condition were 5.5 (2.4-8.6), 5.5 (2.2-8.9) and 0.9 (0.5-1.3) months, respectively (p<0.001). The independent predictive factors of survival after sorafenib failure were poor ECOG (HR 0.801), alpha feto-protein >400ng/ml (HR 0.412) and discontinuation cause (HR 0.349). We further investigated the survival according to patients who received 2nd-line therapy or not. 48 patients were treated with systemic chemotherapy whereas 116 patients received supportive care. Systemic chemotherapy group showed better survival outcome compared to supportive care group (10.6 vs.1.6 months, p<0.001). When terminal supportive care group were excluded, systemic chemotherapy group showed also better survival outcome compared to selected BSC group (10.6 vs.4.2 months, p=0.023).
Conclusions: The survival after sorafenib failure of patients who discontinue sorfenib due to progression and adverse effect was significantly better than due to clinical deterioration. Moreover, patients who received 2nd-line therapy showed better survival than only supportive care after sorafenib failure.
Keywords: HCC, Sorafenib, Chemotherapy

PO - 080

Oral Medications Improve Overall Survival by Enhancing Adherence to Regular Surveillance for Hepatocellular Carcinoma: Results of Mediation Analysis

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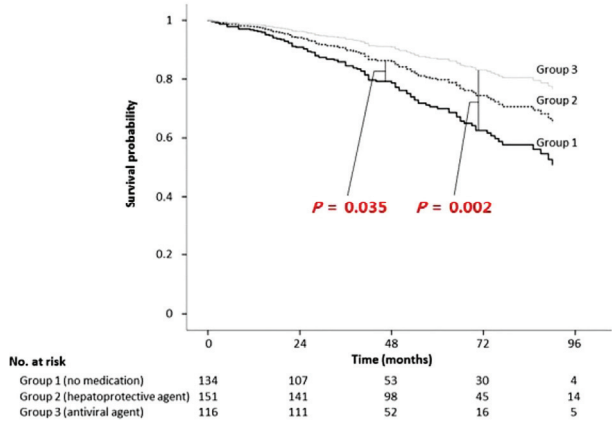

Figure 1.

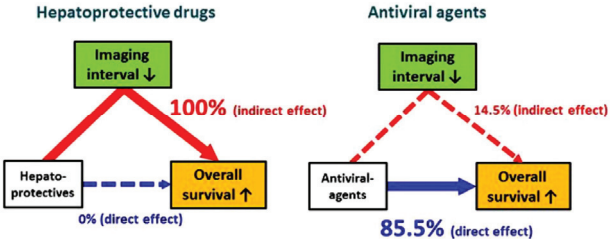

Figure 2.

Aims: Regular surveillance for hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients is essential to detect HCC earlier and to improve prognosis. This study investigated whether prescription of oral medication contributes to adherence to surveillance, early tumor detection, and overall survival (OS).

Methods: A total of 401 CHB patients who were newly diagnosed with HCC were included: 134 patients received no medication (group 1), 151 received hepatoprotective agents such as ursodeoxycholic acid and silymarin (group 2), and 116 received antiviral agents (group 3) at two years before HCC diagnosis. The primary endpoint was OS, and secondary endpoints were compliance to regular surveillance and HCC status at diagnosis.

Results: Compared to group 1, both group 2 and 3 had higher rates of good compliance to regular surveillance (defined as participation in >80% of imaging intervals being ≤6 months) (58.2%, 90.1%, and 97.4%, respectively; P<0.001), more HCC diagnosed at a very early stage (20.9%, 32.5%, and 36.2%; P=0.019) and smaller tumor size (2.8±2.4cm, 1.9±1.1cm, and 1.8±0.9cm; P<0.001). Finally, compared to group 1, both group 2 (hazard ratio, 0.63; 95% confidence interval, 0.41-0.97; P=0.035) and group 3 (hazard ratio, 0.40; 95% confidence interval, 0.22-0.71; P=0.002) had significantly longer OS (Figure 1). In mediation analysis, prolonged OS is resulted considerably from indirect effect mediated by shorter imaging interval (>100% in group 2 and 14.5% in group 3) rather than direct effect of medication itself (Figure 2).

Conclusions: Prescription of oral medication improves compliance to surveillance and enables early detection of HCC, which is finally associated with enhanced survival.

Keywords: Hepatoprotective agents, Antiviral agents, Hepatocellular carcinoma, Surveillance

PO - 081

Comparison of Prognostic Staging Systems for Hepatocellular Carcinoma in a Hepatitis B Virus Endemic Area

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Aims: Many staging systems have been developed for hepatocellular carcinoma (HCC); however, it is uncertain which model provides better information. We aimed to compare performances of 7 prognostic classifications in the prediction of survival among patients with HCC.

Methods: Data of 4,596 randomly selected patients out of 38,167 HCC registrants of the nationwide statutory Korea Central Cancer Registry for 2008 to 2010 were used. A total of 3,962 patients were enrolled and stratified according to the following 5 staging systems and 2 survival prediction models: modified International Union against Cancer (mUICC), Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), Japanese Integrated Staging (JIS), Tokyo Score, Model to Estimate Survival in Ambulatory HCC patients (MESIAH), and Korean version of MESIAH (K-MESIAH). Each model's performance was assessed and compared.

Results: Most patients had preserved liver function (Child-Pugh class A, 71.8%), and 28.2% received curative treatment. As a cause of HCC, 62.2% had hepatitis B virus infection and 10.5% had hepatitis C virus infection. Overall, the MESIAH score had the highest C-statistics (0.797), followed by K-MESIAH (0.792), CLIP (0.762), JIS (0.760), Tokyo Score (0.745), mUICC (0.728), and BCLC (0.727). The likelihood ratio $\chi 2$ value was higher and the Akaike information criterion was lower for MESIAH and K-MESIAH than those for 5 staging systems (LR $\chi 2$; 2,286.04 for MESIAH and 2,365.88 for K-MESIAH; AIC: 36,127.10 for MESIAH and 36,047.24 for K-MESIAH). Of 5 staging systems, mUICC demonstrated the highest C-statistic value for patients with Child-Pugh class A (0.727), and the Tokyo Score had the highest C-statistic value (0.641) for patients receiving curative treatment in subgroup analysis. CLIP showed the highest C-statistics for patients with Child-Pugh class B/C (0.711), patients receiving non-curative treatment (0.729), and patients with HBV infection (0.778).

Conclusions: The MESIAH and K-MESIAH models provided better prognostic stratification for patients with HCC in South Korea.

Keywords: Hepatocellular carcinoma, Staging, Prognosis

PO - 082

Role of Endoscopic Biliary Drainage in Advanced Hepatocellular Carcinoma with Jaundice

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Aims: Advanced hepatocellular carcinoma (HCC) with jaundice has an extremely poor prognosis. In case of obstructive jaundice, biliary drainage can resolve jaundice, but the problem is that obstruction is not evident in many cases. We evaluated the role of endoscopic biliary drainage in patients with advanced HCC with jaundice.

Methods: From 2010 to 2015, total 70 received endoscopic biliary drainage for jaundice due to advanced HCC. Jaundice resolution was defined as follows; complete resolution: total bilirubin less than 2 mg/dl, partial resolution: total bilirubin decreased but > 2 mg/dl.

Results: Child-Pugh class was B in 65.7% (46/70), C in 31.4% (22/70). BCLC stage was B in 14.2% (10/70) and C in 85.8% (60/70). Intrahepatic bile duct dilatation was observed in 50% (35/70) and tumor location were whole liver in 27.1% (19/70) and whole right lobe in 27.1% (19/70). Table 1 showed baseline characteristics of 70 patients. Success rate of biliary drainage was 95% (67/70). After drainage, jaundice was resolved completely in 27.1% (19/70), partially in 28.5% (20/70). The median time to resolution was 19 days (range, 2-96 days). However, in these patients, jaundice was aggravated in 74.3% (29/39) median 88 days (range, 5-399 days) after resolution. The presence of intrahepatic bile duct dilatation was significantly associated with complete resolution of jaundice in multivariate analysis (p=0.040). In overall, 90 days survival rate was 24.2% and median survival was 30 days (95% CI; 9-50 days). Predicting factors for overall survival was jaundice resolution (p<0.001), Child-Pugh class (p=0.019), aspartate aminotransferase (p=0.021) and BCLC stage (p=0.036) in multivariate analysis, respectively.

Conclusions: Through endoscopic biliary drainage, jaundice was improved in 55.7% with advanced HCC and survival can be prolonged in patients who showed jaundice resolution. In jaundice in presence of intrahepatic bile duct dilatation, biliary drainage can be appropriate palliative treatment in advanced HCC patients.

Keywords: Hepatocellular carcinoma, Jaundice, Endoscopic biliary drainage

Table 1. Baseline characteristics

	N =70
Sex (male), n (%)	61(87.1)
Age, years	62.3±9.7
Etiology (A/B/C), n (%)	10/44/16 (14.3/62.8/22.9)
BCLC (A/B/C), n (%)	0/10/60 (0/14.3/85.7)
Okuda (I/II/III), n (%)	1/35/34 (1.4/50/48.6)
Tumor volume (>50%)	35 (50)
PVT, n (%)	47 (67.1)
Metastasis, n (%)	18 (25.7)
Ascites, n (%)	37 (52.9)
Encephalopathy, n (%)	2 (2.9)
Prior HCC treatment history, n (%)	52 (74.3)
Intrahepatic bile duct dilatation, n (%)	35 (50)
Location (Total/Right/Left/Segment 4)	19/19/5/12/(22.9/22.9/7.1/17.1)
Child (A/B/C), n (%)	2/46/22 (2.9/65.7/31.4)
Aspartate transaminase, IU/L	228.8±200.0
Total bilirubin, mg/dL	9.13±5.83
Creatinine, mg/dL	0.87±0.36
C-reactive protein, mg/dL	4.0±3.1
Prothrombin time (INR)	1.36±0.21

Continuous variable, mean±standard deviation

PO - 083

Albumin-bilirubin Grade and Long-term Survival in Very Early Stage Hepatocellular Carcinoma who Received Either Resection or Ablation

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Aims: The Albumin-Bilirubin (ALBI) grade was suggested as a simple, more objective evidence of assessing liver function in hepatocellular carcinoma (HCC). We tested whether ALBI can help stratify long-term outcome after resection or ablation in very early stage HCC.

Methods: A total of 536 HCC patients with the Barcelona Clinic Liver Cancer (BCLC) stage 0 (age = 57.4 ± 10.1; male = 77.6%; hepatitis B virus (HBV) = 80.4%), who received either resection or radiofrequency ablation (RFA) between Jan. 2007 and Dec.2012 at Samsung Medical Center were analyzed. Ideal candidate for resection was defined by normal serum bilirubin and no clinically significant portal hypertension according to BCLC criteria.

Results: ALBI grade, underlying liver disease (HBV or others) and treatment modality (resection vs. RFA) were independent factors associated with survival. Those with ALBI grade 1 showed better 5-year survival rate than grade 2 for patients who received resection (96.8% vs. 92.5%, p = 0.021), as well as patients who received RFA (88.5% vs. 74.9%, p < 0.001), patients with HBV (91.6% vs. 86.5%, p = 0.027), and patients with other liver disease (88.5% vs. 62.5%, p < 0.001). Resection was associated with better survival than RFA (97.4% vs. 88.8% at 5-years, p = 0.012) among ideal candidate for resection (n = 252). Yet, resection was also associated with better survival than RFA in non-ideal candidate for resection (n = 284) (93.6% vs. 79.5% at 5-years, p = 0.004), with ALBI grade 1 (96.8% vs. 88.5% at 5-years, p = 0.007), as well as ALBI grade 2 (92.5% vs. 74.9% at 5-years, p = 0.004).

Conclusions: The ALBI grade was useful for further estimating long-term survival of very early stage HCC who received resection or RFA. However, neither ALBI grade nor BCLC criteria for resection was useful to identify subgroup where less invasive RFA can show similar survival to resection in very early stage HCC.

Keywords: Hepatocellular carcinoma, ALBI grade, Resection criteria

PO - 084

Clinical Outcomes of Intraoperative Radiofrequency Abla-

tion in Hepatocelluar Carcinoma Patients Ineligible for Percutaneous Radiofrequency Ablation or Surgical Resection

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Aims: Intraoperative radiofrequency ablation (RFA) is one of the treatment options for hepatocellular carcinoma (HCC) patients with relatively poor liver function to undergo surgical resection or when percutaneous approach for RFA is not feasible due to the difficult location of the tumor. The aim of this study is to investigate the clinical outcomes of intraoperative RFA compared to surgical resection.

Methods: A total of 76 consecutive patients who received either intraoperative RFA (n=23) or surgical resection (n=53) with curative intent at the Incheon St Mary's hospital from June 2012 to September 2015 were enrolled. Disease free survival and overall survival rates were analyzed.

Results: The median follow-up period was 20.1 months (range, 0.9-41.5). The mean baseline Model for End-Stage Liver Disease (MELD) score was higher in the RFA group compared to the resection group (11.5±4.7 vs. 7.8±1.5, p=0.001). The resection group consisted of larger tumors with the median diameter of 2.7cm (range, 1-16) compared to 2cm (range, 1-5) of the RFA group (p=0.002). However, there was no difference in the number of tumors and the tumor stage between the two groups. The disease free survival rates at 6 and 12 months were 81.6%, 74.8% in the RFA group and 92.2%, 86.2% in the resection group, respectively (p=0.256). The overall survival rates at one year were 91.3% in the RFA group and 94.3% in the resection group, respectively (p=0.635). In the RFA group, 5 patients (21.7%) received liver transplantation (LT) after median interval of 10.9 months (range, 9.2~26.4) since the intraoperative RFA.

Conclusions: The patients who received intraoperative RFA presented with relatively poor liver function but the disease free survival and overall survival rates were non-inferior compared to the patients who underwent resection. Therefore, intraoperative RFA may be considered as a useful option for patients ineligible to percutaneous RFA and surgical resection, or as a bridge therapy before liver transplantation.

Keywords: Intraoperative, Radiofrequency ablation, Resection, Hepatocellular carcinoma

Surgery

PO - 085

Outcomes of Living and Deceased Donor Liver Transplant Recipients according to the MELD Score

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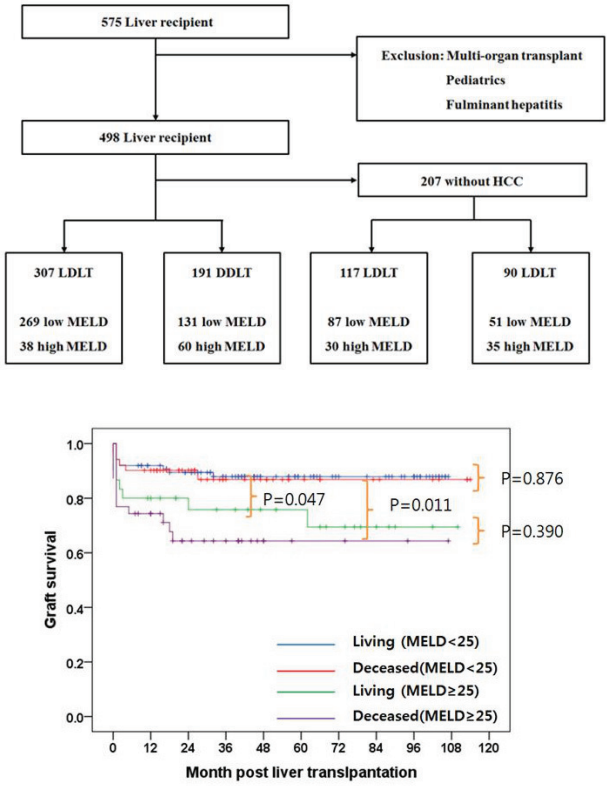

Figure 1. Graft survival of patients without HCC according to MELD score and donor type

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Aims: Living donor liver transplantation (LDLT) has developed as an alternative to decease donor liver transplantation (DDLT) to overcome the critical shortage of deceased organ donations. However, the evidence supporting a LDLT for high model for end stage liver disease (MELD) score recipient is weak. We compared the outcomes of LDLT and DDLT according to MELD scores.

Methods: The study included 498 adult patients who underwent liver transplantation between 2006 and 2014 at Severance Hospital. Patients with re-transplantation and fulminant liver failure were excluded from the study. Recipients were categorized according to their MELD score into low (MELD score ≤25) and high (MELD score >25) MELD group.

Results: About 76.5% of patients are male and median age is 53. Major origin of liver cirrhosis is Hepatitis B virus and 50% of patients had HCC. There were no significant difference gender, donor gender, age, HBV, HCV, HCC and DM. However, age of donor, CTP score and MELD score in DDLT were significantly higher than LDLT. In both LDLT and DDLT groups, patients with high meld score show significantly lower graft survival than patients with low MELD score. (p =0.019 in LDLT and p=0.009 in DDLT) However, in both high and low meld group, there were no significant difference of survival between LDLT and DDLT. Non-HBV, HCC, High MED are risk factor for graft mortality in overall patients. However, HCV and high MELD

are risk factor in patients without HCC.
Conclusions: High MELD score is risk factor for Graft mortality in liver recipients regardless combined HCC. There was no significant difference between LDLT and DDLT, in patients with both high MELD and low MELD. When deceased donor organs are scare, LDLT with donor safety maybe good therapeutic option in patient with high MELD score.
Keywords: Allocation, MELD, Living donor, Graft survival

PO - 086

Transplantation versus Hepatectomy for Hepatocellular Carcinoma 2 cm or Less Than 2 cm

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Aims: Surgical resection has been the treatment of choice for early stage Hepatocellular carcinoma (HCC), and the overall survival was satisfied. However, the postoperative high recurrence rate is a significant problem. The shortage of organ donors has led to a restricted indication for orthotropic liver transplantation for HCC. The aim of this study was to analyze the results of surgical treatment for 2 cm or less than 2cm HCC.
Methods: From January 2005 to December 2013, 619 consecutive HCC patients underwent surgical treatment at our hospital. 119 (19.2%) patients, whose diameter of tumor was 2 cm or less than 2 cm, were included and they were divided into two groups by treatment procedure. One group is hepatectomy group (n=79), the other is transplantation group (n=40). The data were retrospective reviewed in this study.
Results: The median follow-up period was 40 months. Totally, 30 cases experienced tumor recurrence in the follow-up period, 29 of them came from hepatectomy group, while only one case was from transplantation group. Figure 1 show us the treatment methods for recurrent cases after initial hepatectomy. The 1, 3 and 5-year recurrence free survival rates of hepatectomy group were 85.8%, 69.5% and 51.7%, and those of transplantation group were 97.2%, 97.2% and 97.2%, respectively. (P=0.0001) The 1, 3, and 5-year survival rates of hepatectomy group were 97.5%, 93.4% and 90.8%, and those of transplantation group were 90.0%, 87.3%, and 87.3%, respectively. (p=0.819)
Conclusions: Our results show that transplantation could be a radical treatment for 2 cm or less than 2cm HCC.
Keywords: Hepatocellular carcinoma, Transplantation, Hepatectomy

PO - 087

HSV after LDLT

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Aims: Viral infection such as HSV, after Living donor liver transplantation (LDLT) is a major cause of morbidity and mortality that result in injury to allograft rejection and opportunistic superinfection. Most patients undergoing liver transplantation are seropositive for HSV. Without antiviral treatments, reactivated HSV infection develops in as many as 40% of these patients. Anogenital lesions are the second most common presentation of HSV disease in LDLT recipients, and are usually due to reactivation of latent HSV-2 in the sacral ganglia.
Methods: In our clinical experience, i present a case of a 57-year-old female with hepatocellular carcinoma in the outcome of chronic viral hepatitis C who underwent surgery LDLT. ELISA viral panel before surgery: EBV IgG - positive, IgM - negative, HSV IgG- positive, IgM - negative. Her immunosuppressive regimen included - MMF, Tacrolimus, and Prednisone. On the 15th day after the LDLT operation the patient in the pubic region appeared herpes lesion. The level of transaminases in dynamics has increased significantly. Biochemical analysis of blood: ALT - 364 U/l, AST - 98 U/l. GGTP - 159.66 U/l. CRP - 64 ng/ml. Then taken polymerase chain reactions (PCR) analysis for viral infection. PCR for viral panel: HSV DNA 1.2 - detected. CMV DNA - negative. EBV DNA - negative. Given the presence of herpes and PCR data scheduled antiviral therapy - per oral Famvir (Famcyklovir) 1500 mg per day and local Acyklovir ointment.
Results: After the 2 days on the background of anti-viral therapy transaminase levels started to decline over time. Biochemical analysis of blood: AST - 52.80 U/l, ALT - 204.20 U/l, CRP - 11.04 ng/ml. Post operative day (POD) №22, taken PCR for viral panel: HSV DNA 1.2 - negative. CMV DNA - negative. EBV DNA - negative. Antiviral therapy is continued, the dose of Famvir is reduced to 1000 mg per day. On the background of anti-viral therapy marked regression of herpes lesion, transaminase levels declined. Biochemical analysis of blood: AST - 32.80 U/l, ALT - 104.20 U/l. CRP - 3.96 ng/ml.
Conclusions: These Results could help define reasonable indications for transplantation in an era with a shortage of liver grafts related to presented case. Prophylaxis for common infections (HSV and other) in high risk patients improves outcomes in the first year after LDLT. HSV can lead to liver failure after liver transplantation. Antiviral therapy such as Acyclovir, Famcyclavir active against HSV in vitro, and these substances must be used in the treatment of HSV infection after LDLT.
Keywords: Liver Transplantation, HSV, Antiviral therapy, POD after LDLT

PO - 088

LDLT for Non-cirrhotic Portal Hypertension from Cavernous Transformation of Portal Vein - A Case Report

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Aims: Cavernous transformation of the portal vein (CTPV) is a rare condition with various etiologies and diverse clinical presentations.

We present the case of non-cirrhotic young female patient with severe portal hypertension, successfully treated with living donor liver transplantation (LDLT) and the portal inflow was obtained using one prominent collateral vein (engorged paracholedocal vein) from CTPV.

Case presentation: A 23-year-old female without liver cirrhosis was admitted due to upper gastrointestinal hemorrhage at Division of Liver Transplantation and Hepatobiliary Surgery in Ajou University Medical Center. From December 2011 to October 2015, she has experienced 6 times of esophageal varix bleeding and esophageal varix ligation. At the third episode of esophageal varix bleeding, the transjugular intrahepatic portosystemic shunt (TIPS) was tried to reduce the portal pressure but it failed due to inadequate portal vein. A baseline liver biopsy was performed in January 13, 2012. Its finding revealed that fragmented hepatic parenchyma was not cirrhotic or ischemic histological evidence. In addition, there is no histological evidence to suggest vascular obstruction due to thrombosis. At that time, the patient was diagnosed as non-cirrhotic portal hypertension. In October 2015, the patient was recommended the living donor liver transplantation to solve the repeated esophageal varix bleeding from her portal hypertension. Preoperative laboratory data revealed normal liver function. Preoperative esophageogastroduodenoscopy showed esophageal varices, F2 Lm Cb RC (+) without active bleeding. Preoperative multidimensional computed tomography (MDCT) revealed massive dilated paracholedochal vein in the hepatoduodenal ligament and suprahilar area, and splenomegaly was found, too. The donor was her 3-year-older sister. The estimated graft volume of the donor's right lobe calculated by CT volumetry was 679 ml, 63.3% of the whole liver and the estimated graft-to-recipient body weight ratio (GRWR) was 1.41%. Therefore, right lobe graft was planned to transplant on October 21, 2015. Operative finding showed an atretic main portal vein with complex network of tortuous paracholedochal vein, and we performed en bloc hilar dissection of the common bile duct and paracholedochal collateral vein. One thick paracholedochal vein of them looked like an candidate of alternative option for adequate portal inflow. We anastomosed it with donor portal vein in end-to-end fashion. Postoperatve Doppler scan and multi-detector computed tomography showed good portal vein patency to the graft. Six months after the surgery, the patient is doing well with normal liver function.

Conclusions: After dissecting the hepatic artery, en bloc hilar dissection of the common bile duct and paracholedochal collateral vein was successfully performed. The thick paracholedochal vein was an alternative option for adequate portal inflow.

Keywords: Liver transplantation, Cavernous transformation of portal vein, Upper gastrointestinal bleeding, Paracholedochal vein

PO - 089

Changes in T Cells in Peripheral Blood after Adult Liver Transplantation

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Backgrounds: T lymphocytes are an essential component of allograft rejection and tolerance. The aims of the present study are to analyze the characteristics of T cell subsets between deceased donor liver transplantation (DDLT) patients and living donor liver transplantation (LDLT) patients and to investigate the potential role of T cell subsets in cytomegalovirus (CMV) infection, acute rejection, and graft failure.

Methods: Between April 2013 and June 2014, 64 patients underwent adult LT. All patients received basiliximab as induction therapy and tacrolimus as maintenance therapy. The distribution of peripheral blood T lymphocyte subsets pretransplant and 4, 8, 12, and 24 weeks post-transplant were serially monitored.

Results: Patient characteristics did not vary between DDLT and LDLT groups except for Child-Pugh class, model for end-stage liver disease score, and cold ischemic time. However, the Vδ1/Vδ2 ratio in the DDLT group was higher than in the LDLT group (P=0.045). Comparison between LDLT and DDLT groups revealed that CD4+ T cells, CD8+ T cells, CD4/CD8, Vδ1 cells, Vδ2 cells, and γδ T cells did not change significantly over time. The Vδ1/Vδ2 ratio in patients with CMV infection was higher than in patients without CMV infection. The absolute CD3+ and CD8 T cell counts in patients with biopsy-proven acute rejection (BPAR) were higher than in patients without BPAR. The absolute lymphocyte counts, CD4+ T cell, γδ T cell, and Vδ2 γδ T cell counts in patients with graft failure were lower than in patients without graft failure.

Conclusion: CD3+ T cells are different between DDLT and LDLT groups. Patients with BPAR showed elevated CD3+ and CD8+ T cells. The present study suggests that LDLT patients receive high doses of immunosuppression compared with DDLT patients. Vδ2γδ T cells are closely associated with CMV infection and graft failure.

Keywords: Liver transplantation, T lymphocyte, Cytomegalovirus infection, Graft failure, Biopsy-proven acute rejection

Surgery

PO - 090

Relevance of the Tumor Site and Node Metastasis in Patients with Intrahepatic Cholangiocarinoma

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Aims: Although node metastasis is a well-known prognostic factor of intrahepatic cholangiocarcinoma (IHCC), relationship between tumor site and metastatic node is rarely reported. In this study, we compared the metastatic node and oncologic outcomes between perihilar and peripheral IHCC.

Methods: The study population included 31 patients with IHCC who underwent potentially curative resection in tertiary university hospital. We respectively analysed pathologic and survival data between near-hilar (n = 7) and peripheral (n=24) IHCC.

Results: There were no significant differences in the preoperative and intraoperative data between two groups. Near-hilar IHCC group

showed higher rate of R1 resection (28.6 % vs 0 %, p = 0.045), perineural invasion (57.1 vs 6.3 %, p = 0.017), and node metastasis (66.7 vs 6.3 %, p = 0.009). Median follow up period was 22 months and the 3-year overall survival (OS) was 72.7 %. There was no significance in 3-year OS (45.7 vs 64.8 %, p = 0.206). However, near-hilar IHCC group showed lower 3-year recurrence free survival (0 vs 32.0 %, p=0.046) compared with peripheral IHCC group.

Conclusions: Near-hilar IHCC group showed more frequent node metastasis and recurrence after resection compared with peripheral IHCC. IHCC around hepatic hilum needs regional lymph node dissection with hepatectomy.

Keywords: Intrahepatic cholangiocarcinoma, Liver resection, Oncologic outcome, Tumor site

PO - 091

The SUV on 18F-FDG-PET/CT Imaging as an Independent Predictor for Overall Survival and Disease Free Survival after Hepatectomy of HCC (Less than 5 cm)

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Aims: 18F-Fluoro-deoxyglucose (FDG) PET/CT can be used to monitor the biological behavior and predicts clinical outcome in patients with hepatocellular carcinoma (HCC). The purpose of this study was to evaluate whether standardized uptake value of the tumor (SUV) could predict the risk of recurrence and death for the HCC (less than 5cm) patient after hepatectomy.

Methods: Retrospective analysis was performed on a database of HCC patients who underwent hepatectomy between November 2008 and December 2014. The cutoff values of SUV which calculated from FDG uptake were decided by receiver operating characteristic (ROC) curve analysis. Univariate and multivariate regression analysis were performed to identify predictive factors of recurrence and death.

Results: A total of 216 patients were included in the present study. The median follow-up period was 32.5 months (Range, 82). The 1, 3, 5 years cumulative overall survival rates and disease free survival were 94.8%, 90.3%, 90.3% and 81.6%, 64.4%, 56.3%, respectively. The cutoff value of SUV was 4.75 (AUC=0.701, P=0.004) which defined by ROC curve analysis. The high SUV (≥4.75) was found to be independent factor for disease free survival in multivariate regression analysis. And high SUV (≥4.75) and large tumor size (≥3.75) were found to be independent factors for overall survival in multivariate regression analysis.

Conclusions: The high SUV (≥4.75) on 18F-FDG-PET/CT imaging was an independent and significant predictor for overall survival and disease free survival for the HCC (less than 5cm) patient after hepatectomy.

Keywords: Hepatocellular carcinoma, PET CT, Survial

PO - 092

Case-control Study of Pure Laparoscopic Hemihepatectomy vs. Open Left Hemihepatectomy for Hepatocellular Carcinoma

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Purpose: The objective of this study was to compare the outcomes of pure laparoscopic left hemihepatectomy (LLH) versus open left hemihepatectomy (OLH) for hepatocellular carcinoma (HCC) in case-control design.

Methods: Forty six patients who underwent LLH for HCC between December 2007 and December 2015 in a tertiary referral center were included in this retrospective study. Sixty patients who underwent OLH during the same period were matched to LLH for demographics, preoperative data, and tumor characteristics and the clinical perioperative outcomes between the two groups were compared.

Results: The mean operative time was longer in LLH group compared with the OLH group with statistical significance (210.06±53.12 min vs 167.04±65.19 min, p=0.007). However, the mean operative time of the last ten cases each of LLH and OLH had no significant difference (160.70±65.19 min vs 167.04±65.19 min, p=0.74), and LLH group had shorter hospital stay (8.47±1.59 days vs 12.54±3.20 days, p=0.01). There was no open conversion case and only one postoperative complication which was mild ileus in the LLH group.

Conclusion: Pure laparoscopic left hemihepatectomy for hepatocellular carcinoma was safe and feasible procedure for selected patients.

PO - 093

The Role of Curative Intent Surgical Resection for the Recurrent HCC

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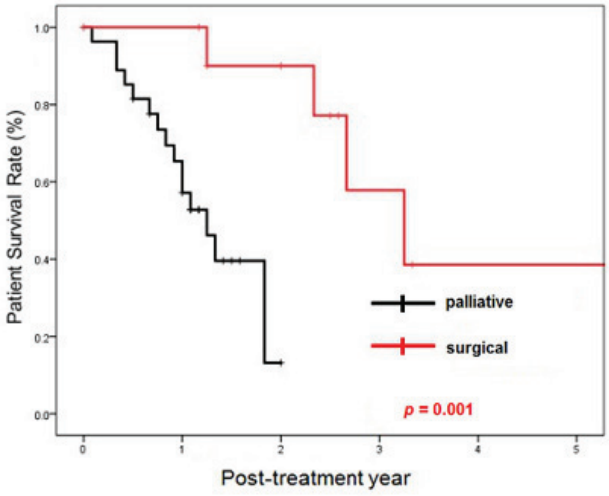
Aims: Liver transplantation (LT) is one of the best treatment for hepatocellular carcinoma. However, there could be HCC recurrence in around 10-20% of the transplant patients. The Recurrent Hapatocellular carcinoma (HCC) after liver transplantation remains one of the major causes to graft failure and patient death. Because HCC recurrence is known for systemic disease, systemic therapy may be considered. However the optimal treatment of recurrent HCC is not established. The aim of this study is to evaluate the difference of graft survival rate between palliative therapy and curative intent surgical therapy after LT.

Methods: A total 292 recipients with HCC who underwent liver transplantation between January 2007 and April 2015 in Severance hospital were retrospectively reviewed. Among 292 patients, 41 patients developed hepatic or extra-hepatic recurrent HCC. We compared the outcomes of the recurred patients according to the therapeutic approaches.

Table 1. Patient and tumor data

	HCC recur (n=37)	No HCC recur (n=192)	p-value
Age(mean ± SD)	50.9 ± 6.17	54.4 ± 6.8	0.004
Sex (M/F) %	32/5	156/36	0.447
Etiology (%)			0.357
HBV	33(86.8%)	158(82.7%)	
HCV	3(7.9%)	18(9.4%)	
HBV + HCV	1(2.6%)	1(0.5%)	
Alcoholic	0(0%)	10(5.2%)	
Other	0(0%)	5(2.6%)	
AFP	292.8 ± 622.2	50.4 ± 223.79	0.001
Criteria			0.001
Milan	19(51.4%)	158(82.3%)	
UCSF	6(15.8%)	9(4.7%)	
>UCSF	12(32.4%)	25(13.1%)	



Results: The mean age of the HCC recurrence group was younger than non-recurrence group (51.4 ± 6.3 vs 54.8 ± 6.9, p<0.003). There was no significant difference of the etiology of HCC between the groups. The patients above Milan criteria showed a higher tumor recurrence rate than those within Milan criteria(Odd ratio 4.717, p<0.001). The curative intent surgical therapy was performed in 13 patients. Among them, resection only in 2, adjuvant chemotherapy after resection in 4, adjuvant radiation therapy (RT) in 4, adjuvant transarterial chemoembolization (TACE) and chemotherapy in 1, adjuvant TACE and RT in 1, and adjuvant TACE and RFA in 1 case. The palliative therapy was consisted of TACE, chemotherapy, or RT. Among the patients received curative intent surgical therapy, 3 patients had intrahepatic recurrence and 10 patients had extrahepatic recurrence.

The 5 year graft survival was higher in curative intent surgical therapy group than in palliative therapy group (51.1% vs 306%, P=0. 026).

Conclusions: The curative intent surgical therapy showed the superior graft survival than palliative therapy. The curative intent surgical therapy is not applicable in every recurrent case. However the patient received curative intent therapy if possible, it is increased with the graft survival significantly.

Keywords: Liver transplantation, Hepatocellular carcinoma, Recurrent hepatocellular carcinoma

Poster Exhibition

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Alcoholic Liver Disease

PE - 001

Outcome of Deceased Donor Liver Transplantation for Alcoholic Liver Disease

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Aims: Alcoholic liver disease (ALD) is the second leading indication for liver transplantation (LT) in the United States and Europe. In Korea, there has been a gradual increase in number of patients with ALD. Now ALD is the second most common indication for deceased donor LT (DDLT), but there is no strict guidelines or regulations such as minimum of 6 month's abstinence before transplantation. Moreover, little is known following the post-transplant outcomes for ALD in Asian countries. The aim of this study is to assess the post-DDLT survival outcome and evaluate the factors associated with survival rates of DDLT for ALD patients compared with HBV patients.

Methods: The results were retrospectively reviewed from 272 patients, who underwent DDLT from January 2010 to Dec 2014 at Seoul National University Hospital.

Results: Alcohol group had less cases with HCC (8.8% vs. 46.4%, p<0.001), high MELD (25.6±8.0 vs. 22.2±8.8, p=0.046), and high CTP score (11.6±1.0 vs. 10.7±1.7, p<0.001). There were more admission cases for abnormal liver function test (30.3% vs. 14.4%, p=0.040) and more psychiatric problems (36.4% vs. 9.5%, p=0.001) in ALD group. There was no survival rate difference between two groups (p=0.907). In univariate analysis, post-LT 7day GGT was the only factor to be statistically significant (p=0.023). In non HCC group, the hospital day was longer (32.2±24.7 vs. 21.0±15.1, p=0.025), more cases show fatty change in post-LT 1yr biopsy (40.0% vs. 9.1%, p=0.040).

Conclusions: In conclusion, despite no difference in overall survival, careful management after DDLT including psychiatric problem would be needed in ALD group.

Keywords: Alcohol, Cirrhosis, Liver transplantation, Deceased donor liver transplantation

PE - 002

Liver Transplantation for Alcoholic Liver Disease

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Aims: The most commonly affected organ remains the liver with a risk of alcoholic liver disease (ALD) which can range from asymptomatic to alcoholic hepatitis to alcoholic cirrhosis. Alcoholic liver disease (ALD) is the third most common diagnosis among patients which operation is required liver transplantation (LT) in the Kazakhstan. Pretransplant abstinence broadly achieves two goals; it allows a window of opportunity for the liver to stabilize, and it allows opportunity to examine the patient's commitment.

Methods: In our center, liver transplant from a living donor to3 recipient with alcoholic liver disease in the outcome of liver cirrhosis. For the 6-8 months prior to the hospitalization of the patient during abstinence, it is important for patients who are prepared for orthotropic liver transplantation (OLT).

Results: Indications for OLT was Child-Turcotte-Pugh score >7 with single episode of spontaneous bacterial peritonitis andan estimated 1 year survival without transplantation.

Conclusions: ALD is an acceptable indication for liver transplantation as survival of these patients after transplantation is similar to that seen in patients who receive grafts for other causes. Patient selection is important for rationing scarce organs, hence the use of prognostic models for predicting risk of relapse to alcoholism. Rate of graft loss is no greater and rejection of the graft is even less so in patients transplanted for ALD.

Keywords: Alcoholic liver disease, Orthotopic liver transplantation, Pre-transplant abstinence, Living donor liver transplantation

PE - 003

Predictive Factors of Death or Transplantation in Patients with Severe Alcoholic Hepatitis Treated with Prednisolone

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Aims: Corticosteroids have been shown to significantly decrease short-term mortality in severe alcoholic hepatitis with Maddrey's discriminant function (MDF) score ≥32. However, independent clinical factors associated with unfavorable outcome during steroid therapy are not known definitely. The aim of this study was to investigate predictive factors associated with death or liver transplantation in patients with severe alcoholic hepatitis treated with prednisolone.

Methods: A total of 134 consecutive patients treated with prednisolone for severe alcoholic hepatitis (MDF score ≥32) in Asan Medical Center between May 2004 and May 2014 were evaluated retrospectively. Survivals at 28 days were compared by Kaplan-Meier curve and log-rank test. The risk of death or transplantation was assessed by the Cox proportional hazards regression model.

Results: The median age of the patients was 48 years (range, 24-73), and 105 (78.4%) patients were male. During the 28 days period, 11 patients (8.2%) died, 10 (7.5%) received a liver transplant. The median follow-up duration was 5.3 months. Sex, hepatic encephalopathy, Model for End-stage Liver Disease (MELD) score, MDF at 7days, and early change bilirubin levels (ECBL) at 7 days were predictive factors by univatiate analysis. In multivariate analysis, female (HR, 3.023; 95% CI, 1244-7.347, p=0.015), MELD score >25 (HR, 3.238; 95% CI, 1.169-8.972, p=0.024), and absence of ECBL at 7dyas (HR, 6.579; 95% CI, 1.513-28.571, p=0.012) were highly associated with the risk of death or transplantation.

Conclusions: Our study revealed that female, MELD >25 and absence of ECBL were poor predictive factors in patients with severe alcoholic hepatitis although they were treated with prednisolone. Especially,

these patients need to be assessed and prepared for the liver transplantation.
Keywords: Alcoholic hepatitis, Survival, Corticosteroid, Risk factor

PE - 004

The Frequency of Peripheral CD1d+ NKT Cell Can Be Biomarker for Steroid Therapy in Patients with Severe Alcoholic Hepatitis

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Aims: Natural killer T (NKT) cells can be divided into two types broadly. One of them is invariant NKT cells (iNKT) and these cells have CD1d molecules that were presented from antigen presenting cells. Also, CD1d is generally known to present by inflammatory events in patients with alcoholic liver disease. Thus, we investigated the characteristics of peripheral CD1d-restricted T cell population in patients with severe alcoholic hepatitis (SAH).
Methods: Four patients with SAH and four healthy people were enrolled. Peripheral blood mononuclear cells were isolated from these subjects according to time schedule, baseline (W0) and after 1 week (W1). To detect iNKT cells, lymphocytes were stained with CD1d Alpha Gal Cer tetramers (Proimmune, oxford, UK) for 30 minutes. We investigated the difference of CD1d-restricted T cells population with positive CD3 and negative CD19 between SAH patients and healthy controls. Flow cytometric analysis was performed using BD FACSCanto II.
Results: The baseline frequencies of peripheral CD1d+, CD3+, CD19- NKT cell in patients with SAH were lower compared to those of healthy controls. There were two types of changing pattern of peripheral CD1d+ NKT cell in patients with SAH. First is increasing pattern of peripheral CD1d+ NKT cell at W1 compared to W0 (SAH 1 group). The second is decreasing pattern of peripheral CD1d+ NKT cell at W1 compared to W0 (SAH 2 group). SAH 1 group showed marked improvement of clinical parameters without steroid therapy but, SAH 2 group needed steroid therapy usually for clinical improvements.
Conclusions: Based on above results, we consider that frequency of peripheral CD1d+ NKT cell can be used as biomarker for steroid treatment of patients with SAH patients.
Keywords: Severe alcoholic hepatitis, NKT cell

Cell Biology / Molecular Biology

PE - 005

Genetic Alterations of the SIAH-1 Gene in Hepatocellular Carcinomas

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Aims: Siah-1 is the mammalian homolog of Drosophila seven in absentia (sina) and has been identified as a p53-inducible gene. Siah-1 can induce cell cycle arrests, tumor suppression, and apoptosis through a novel β-catenin degradation pathway.
Methods: To determine whether genetic alterations of Siah-1 gene are involved in the development and/or progression of HCCs, we searched for mutation of the Siah-1 gene in 38 HCCs by single strand conformational polymorphism and sequencing. The effect of Siah-1 on β-catenin degradation was further examined in wild- and mutant-type Siah-1 transfected HEK 293T cells.
Results: We found two frameshift mutations and one missense mutation of the Siah-1 gene. The cases with Siah-1 mutation showed nuclear translocation and cytoplasmic staining of β-catenin. Interestingly, three mutants of Siah-1 stabilized cytoplasmic levels of β -catenin, even after treatment of adriamycin. Furthermore, Three mutants failed to suppress cyclin D1 expression and to induce apoptosis.
Conclusions: These data suggest that inactivating mutations of the Siah-1 may contribute to the development of HCCs through β-catenin stabilization and apoptosis block.
Keywords: HCC, β-catenin, P53, Cyclin D1

PE - 006

Inactivating Mechanism of ATBF1 Gene in Hepatocellular Carcinomas

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Aims: Alpha-fetoprotein (AFP) is frequently detected in hepatocellular carcinomas (HCCs) and AT motif binding factor 1 (ATBF1) down-regulates AFP gene expression in hepatic cells. The ATBF1 gene also inhibits cell growth and differentiation and altered gene expression is associated with malignant transformation.
Methods: To investigate the potential role of the ATBF1 gene in HCCs, we analyzed somatic mutations, allelic loss and hypermethylation of the ATBF1 gene in 45 sporadic HCCs. The level of ATBF-1 mRNA expression was analyzed using quantitative real-time RT-PCR.
Results: Genetic studies of the ATBF1 gene revealed absence of a somatic mutation in the hotspot region and 5 (16.7%) of 30 informative cases showed allelic loss at the ATBF1 locus. Hypermethylation in the intron 1 region of the ATBF1 gene was detected in only one case. Interestingly, ATBF1 mRNA expression in HCCs was significantly reduced in 33 (73.3%) samples compared to the corresponding surrounding liver tissues.
Conclusions: These results suggest that the ATBF1 gene may contribute to the development of HCCs via transcriptional down-regulation of mRNA expression, but not by genetic or epigenetic alterations.
Keywords: Alpha-fetoprotein, ATBF1, Genetic alteration, Expression

PE - 007

WT1 Is the Regulatory Gene in the Process of Hepatocyte-like Cells Differentiation from Bone Marrow Mesenchymal Stem Cells

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Aims: Bone marrow-derived human mesenchymal stem cells (BM-hMSCs) have been known to differentiate into multi-lineage cell types and used for differentiated hepatocyte-like cells. The mesenchymal-epithelial transition (MET) plays as a key of cellular transdifferentiation programs, including wound healing and tissue regeneration. Wilms' tumor suppressor gene (WT1) controls transitions between the mesenchymal and epithelial state of cells. The purpose of this study is to clarify underlying differentiation mechanism and function of WT1 by screening the key factors in hepatic differentiation stem cells.

Methods: To detect the regulatory gene of BM-hMSC into functional hepatocytes, protein/DNA array was performed in BM-MSCs before and after differentiation. Hepatic differentiation of BM-hMSCs was evaluated using RT-PCR, western blotting, periodic acid-schiff staining, and a urea synthesis assay. To determine the effect WT1, during induction of hepatic differentiation from BM-hMSCs which were transfected with WT1 siRNA and identified through the change of liver specific genes, transcription factors, and MET markers using RT-PCR and western blotting in WT1-knockdown BM-hMSCs.

Results: Here, we demonstrate that WT1 increases during hepatic differentiation of BM-hMSCs. Differentiated hepatocyte-like cells changed in morphology, function and hepatic gene expression. Also, the expressions of epithelial markers were increased, while the expressions of mesenchymal markers were decreased. In contrast, down-regulation of WT1 reduced hepatic differentiation. The mRNA expression of Albumin and TAT was decreased in the WT1-knockdown BM-hMSCs during hepatic differentiation. Furthermore, down-regulation of WT1 increased the expression of mesenchymal markers but decreased the expression of epithelial markers. Also, during the hepatic differentiation, WT1-knockdown BM-hMSCs didn't change in morphology, looked spindle or fusiform shape.

Conclusions: In this study, we identified novel factors in the process of hepatic differentiation by MET. Our results demonstrate that BM-hMSCs may be a source of cells for liver regeneration and provide the mechanism of liver regeneration through MET process by the WT1.

Keywords: Wilms' tumor suppressor gene (WT1), Bone marrow-derived human mesenchymal stem cells (BM-hMSCs), Mesenchymal-epithelial transition (MET), Hepatic differentiation

PE - 008

Calcium Mobilization through L-type Channels in Hepatic Stellate Cell Is Essential for TGF-b-mediated CTGF

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Aims: In hepatic fibrogenesis hepatic stellate cell (HSC) is a major cell type responsible for producing a major profibrogenic cytokine TGF-b, and connective tissue growth factor (CTGF), a major fibrogenic mediator in several organs. The multi-functional nature of TGF-b signaling in hepatic fibrogenesis is still elusive. At the previous The Liver Week(2015) we reported that Pyk2 is essential for TGF-b-mediated, Smad-independent CTGF induction. Pyk2 is known to be calcium-sensitive, and TGF-b was reported to increase intracellular calcium level. Therefore, we investigated the relation between intracellular calcium levels and pro-fibrogenic TGF-b/Pyk2 axis in hepatic stellate cell.

Methods: Immortalized human stellate cell line, LX-2, has been cultured. After TGF-b treatment, expression of CTGF and a-SMA were assessed with RT-PCR and western blot. Pharmacological inhibitor and siRNA-mediated knockdown were used to modulate the activities and expression levels of protein. Intracelllular calcium mobilization was measured with Fura-4/AM. Activation of Pyk2 was addressed in western blot using different phosphorylation site-specific antibodies.

Results: CTGF expression was up-regulated within 1hr in TGF-b stimulated LX-2. This up-regulation was greatly suppressed by siRNA-mediated knockdown and pharmacological inhibitor of Pyk2. TGF-b treatment increased phosphorylation of Pyk2 on tyrosine 402, 579/580, and 881. Consistent with the previous reports, TGF-b increased intracellular calcium concentration in Fura-4-preloaded LX-2. CTGF induction by TGF-b was blocked in dose dependent manner by pre-treatment with BAPTA-AM, an intracellular calcium chelator, while A23187, a calcium ionopore, increased CTGF induction even in the absence of TGF-b, suggesting that increase of intracellular calcium level is enough to induce CTGF expression. In addition, A23187 increased phosphorylation of Pyk2, and CTGF induction by A23187 is also greatly reduced by siRNA of Pyk2. Pre-treament of LX-2 with Nifedipine (an L-type calcium channel blocker) suppressed CTGF induction by TGF-b in dose-dependent manner, while FPL64176 (L-type channel activator) increased CTGF expression without TGF-b. The CTGF up-regulations by TGF-b, A23187, and FPL64176 were all suppressed by siRNA-mediated knockdown and pharmacological inhibitors of Pyk2.

Conclusions: In hepatic stellate cell, TGF-b increases the intracellular calcium level through L-type calcium channel, leading to downstream Pyk2 signaling for CTGF induction.

Keywords: Fibrosis, TGF-b, Pyk2, Calcium

PE - 009

3D Printing of Mouse Primary Hepatocytes for Generating 3D Hepatic Structure

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Purpose: Liver transplantation is the most clearly available treatment for severe liver disease. However, it is limited by donor organ shortage and donor pool. Recently, it is suggested that development of feasible technique isnecessary to overcome such limitation. Here, we suggest 3-dimentional (3D) bioprinting technique as one of the mostpromising techniques.

Methods: To isolate mouse primary hepatocytes, collagenase was injected into 4-6 weeks mouse liver. Isolated hepatocytes were stained albumin, HNF4alpha and Hepar1 for confirming hepatocytes. Primary hepatocytes were mixed with 3% alginate and printed using 3D printer (made by KIMM). 3D printed hepatic structures were cultured with hepatocyte long term culture media, and its function and gene expression were conducted by qRT-PCR. To compare primary hepatocyte function, primary hepatocytes were also cultured bys and wich method and 2D. Sand wich cell culture used on a single surface was overlaid with a second layer of extracellular matrix, and 2D cell culture used on single surface was dry coating. cultured with hepatocyte long term culture media, and its function and gene expression were conducted by qRT-PCR.

Results: We set up mouse liver perfusion system for isolating primary hepatocytes. Two-step colloagenase methodefficiently isolated primary hepatocytes (8X107 cells/mice). Our methods could isolate hepatocytes with 70~80% viability. These hepatocytes were immuno-stained and qRT-PCRwith albumin, CK18 for confirming functional hepatocytes. Isolated hepatocytes were highly expressed albumin and CK18 but not expressed AFP. To imitate functional liver organ,we made 3D hepatic structure (25×25mm) with primary hepatocytes using 3D bioprinter. Surprisingly, the cellswere survived more than 30 days in alginate structure without any morphological change as compare to collagen sandwich or 2D cultured cells. In addition to morphology of 3D printed hepatocytes, hepatic marker genes were still expressed.

Conclusions: These results provide the methods for primary hepatocyte long-term culture and possibility of mimicking 3D liver structure. Also, this is suggesting a proof of in vivo-like morphology of a transplantable liver graft to be a potential treatment for liver disease.

Drug and Toxic Injury

PE - 010

ZLITHAMACR

Byung Seok Lee, Seok Hyun Kim, Eaum Seok Lee, Ju Seok Kim, Jong Seok Joo, Hae Jin Shin, Hyuk Soo Eun, Woo Sub Kim

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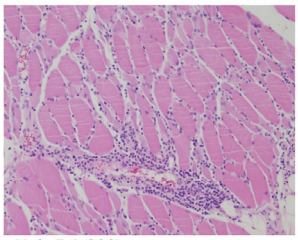
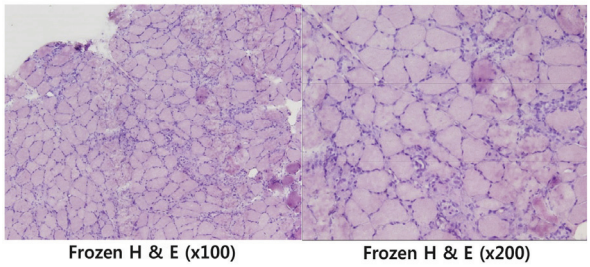
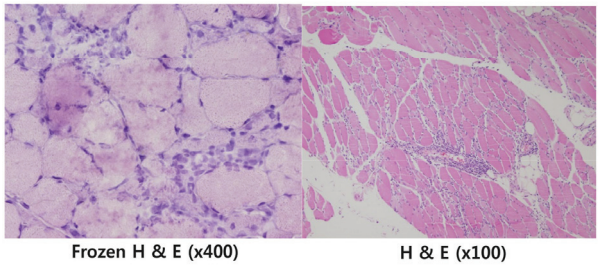
Aims: To alert all the people to recklessly consuming herb medicines. Herbs are widely used in oriental medicine to treat various symptoms in South Korea. But, very few toxic effects have been described.



H & E (x200)



Frozen H & E (x100) Frozen H & E (x200)



Frozen H & E (x400) H & E (x100)

Zizania latifolia, known as Manchurian wildrice is a plant easily accessible in rural areas in South Korea. It is believed that Zizania latifolia has beneficial effects for immunity, detoxification function, diabetes mellitus, arthritis as a folk remedy. Medicinal herb-induced liver injury reported on the literature ranges from mild elevation of liver enzymes to fulminant liver failure and liver cirrhosis. However, the toxicity of Zizania latifolia has not yet been described in the literature. A 57-year old woman was admitted to our hospital with the presentation of nausea, jaundice, generalized weakness, proximal muscle weakness that started from 1 to 2 weeks after consuming boiled wild rice. Laboratory investigations, imaging study, muscle biopsy were performed. The overall history, clinical manifestations and results of laboratory findings, histological findings, imaging study all are indicative of the diagnosis of Zizania latifolia-induced toxic hepatitis and symmetrical myopathy. She revealed fairly elevated aspartate aminotransferase: 1266U/L, alanine aminotransferase: 630U/L, total bilirubin: 11.1mg/dL, alkaline phosphphatase: 218U/L, lactate dehydrogenase: 2674U/L, creatine kinase: >15000U/L levels at peak hours. The recovery of her symptoms and elevated laboratory findings to some degree took approximately 2 weeks. She got discharged after 2 weeks of hospitalization with remaining mild muscle weakness and laboratory results of aspartate aminotransferase: 136U/L, alanine aminotransferase: 22U/L, total bilirubin: 5.5mg/dL, alkaline phosphphatase: 188U/L, lactate dehydrogenase: 673U/L, creatine kinase: 107U/L. Her follow-up 10 days after discharge showed remaining mild muscle weakness and still elevated laboratory findings. She has still been followed up. Here we report a rare case of Zizania latifolia-induced toxic hepatitis and myopathy to alert all the people to recklessly consuming herb medicines.

Keywords: Zizania latifolia, Wild rice, Toxic hepatitis, Myopathy

Genetic

PE - 011

The Major Changes of Gilbert's Syndrome and UGT1A1 Gene Abnormalities in Mongolians Are Western Type

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Aims: Hereditary abnormalities of uridinediphosphoglucuronate-glucuronosyltransferase 1A1 (UGT1A1) gene is the major cause of unconjugated hyper-bilirubinemia. The abnormalities of UGT1A1 gene in Mongolian population remain uninvestigated. Eight in 99 consecutive Mongolian adults developed indirect hyperbilirubinemia. We therefore studied Mongolian patients for GS and UGT1A1 abnormalities.

Methods: Between 2007 and 2014, ninety-nine consecutive Mongolian adult patients of chronic liver disease from the Department of Gastroenterology, Mongolian National University of Medical Sciences were studied. Eight (8.1%) of them developed indirect hyperbilirubinemia. All patients were tests for blood chemistries, hemoglobin, international normalized ratio (INR), mean corpuscular volume (MCV), glucose-6-phosphate dehydrogenase (G6PD) levels as well as UGT1A1 genetic abnormalities. We genotyped the UGT1A1 gene for the $A(TA)_6TAA$ (6) or $A(TA)_7TAA$ (7) promoter variant, and the coding region for nucleotide mutations (nt)-211 G to A, nt-686 C to A, nt-1091 C to T and nt-1456 T to G.

Results: Among the eight patients that developed indirect hyperbilirubinemia, six were male and two were female. All patients had hemoglobin, INR, MCV and G6PD levels within normal limit and we excluded possibility of anemia, decompensated liver function, thalassemia and G6PD deficiency. Our data confirms two variants of the UGT1A1 gene among the Mongolian patients. Two case were homozygous for nt-211G>A mutation, two case heterozygous for 6/7 promoter variants and nt-211G>A mutation, whereas four case were typical GS with homozygous 7/7 promoter genotype with no mutation in the coding region None of our Mongolian patients had mutations at nt-686, nt-1091 or nt-1456.

Conclusions: Our pilot results show that GS and UGT1A1 abnormalities are common in Mongolians. Prevalence of the UGT1A1 promoter abnormalities in Mongolians are similar to the Western population; whereas the high prevalence of nt-211G>A variant is similar to the Asians. Further studies with much larger number of patients are necessary to confirm the genetic status of GS and UGT1A1 variants in Mongolians.

Keywords: Gilbert's Syndrome, UGT1A1 gene, Hyper-bilirubinemia, Mongolia

PE - 012

Genes Associated with Prognosis of Hepatocellular Carcinoma: Validation of Microarray Results Using Quantitative Real Time RT-PCR

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Aims: In the previous array-based analysis of gene expression and DNA methylation associated with recurrence of HCC, up-and down-regulating genes affecting on the HCC recurrence were extracted, that was reported already by our cooperative group.

Methods: In this study, we validated the down-expressed and hyper-methylated genes (MRPL4, PCDHB11, SN2, CYGB, HSD17B6) and an overexpressed and hypo-methylated gene(NMB) in independent cohort(n=90) using HCC tissues and paired normal liver tissues collected from multicenter in Korea. We measured gene expression of the six genes using real time RT-PCR from the normal and HCC tissues, analyzed correlation of prognosis and gene expression between tumor and non-tumor tissues using student t-test and their prognostic significance using Cox regression analysis.

Results: Out of six genes, CYGB and PCDHB11 were little expressed in both tumor and non-tumor, which is not consistent with our previous result. In apart, GPSN2 and MRPL4 were over expressed in tumor tissues in comparison to normal.($p<0.0001$) However NMB was overexpressed in tumor tissue than in non-tumor tissue.($p=0.0002$) as same as the previous result. HSD17B6 was down-regulated, but is not significant ($p=0.5980$), in tumor tissues compared to the non-tumor tissues.

Regarding three significant genes(GPSN2, MRPL4, NMB) in t-test, the patients who have low expression of GPSN2 has shown higher recurrence rate($p=0.0458$), the patients who have higher expression group of MRPL4 shows higher recurrence rate.($P=0.0385$). The high expression group of NMB shows higher recurrence rate ($P=0.04417$) and shorter disease free survival rate($P=0.168$)

In the univariate cox-regression analysis of significant genes and clinical parameters, GPSN2, MRPL4 and NMB were significant with Edmonson-Steiner grade, HBV positivity, high AFP level, tumor state and vascular invasion. In multivariate analysis, only NMB was an independent prognostic factor.($p=0.031$)

Conclusions: In our study of gene expression and its correlation with clinical markers on the basis of microarray thereafter with quantitative assay of the specific markers, validation is very important for the next step validation with high volume data set. A gene that we validated may have significant role in the prognosis of HCC.

Keywords: HCC, Gene, Prognostic factors, Methylation

PE - 013

Severe Indirect Hyperbilirubinemia Patient with NT-211G>A Variant of UGT1A1 Gene

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Aims: Hereditary abnormalities of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene is associated with unconjugated hyper-bilirubinemia worldwide.

Methods: Here we report one case of rapid onset of severe hemolysis and severe indirect hyperbilirubinemia in patient with nt-211 G>A mutation in UGT1A1 gene during the initial phase of combined interferon and ribavirin therapy for chronic viral hepatitis C. A 23-year-old Mongolian male developed chronic viral hepatitis C three years ago. His baseline laboratory data were hemoglobin 16.1 g/dl, MCV 86.8 fL, prothrombin time INR 1.0, AST 27 IU/L, ALT 27 IU/L, total bilirubin 1.4 mg/dL, direct bilirubin 0.4 mg/dL. His HCV RNA was genotype 1b and viral load was 3,063,289 IU/mL. The analysis of UGT1A1 gene revealed a homogeneous nt-211 G to A mutation. In the second week of the combined Peginterferon alfa-2a 100mcg plus Ribavirin 1200mg therapy, the patient developed increased jaundice with total bilirubin 4.9 mg/dL, direct bilirubin 1.9 mg/dL, hemoglobin 14.0 g/dL. Reducing the dosage of Ribavirin to 1000 mg daily, the total bilirubin went down to 1.9 mg/dL, direct bilirubin 0.9 mg/dL, hemoglobin 11.0 g/dL and HCV RNA became undetectable in the fourth week. The dosage of Ribavirin was further reduced to 800 mg daily. The total bilirubin level remained steady at 1.9 mg/dL, direct bilirubin 0.6 mg/dL and hemoglobin 10.4 g/dL in the eighth week. In the 22nd week, the patient is discontinued from the combination therapy due to severe depression, and the total bilirubin was 1.2 mg/dL, direct bilirubin 0.4 mg/dL and hemoglobin 11.4 g/dL. The patient achieved a sustained virological response despite the early termination of the combination therapy.

Results: The hemolysis was improved by reducing dosage of ribavirin. The patient had sustained virological response despised the severe indirect hyperbilirubinemia.

Conclusions: UGT1A1 abnormalities should be assessed when hyperbilirubinemia is observed during the initial phase of combined interferon and ribavirin therapy.

Keywords: UGT1A1 gene, Hyperbilirubinemia, NT-211G>A

PE - 014

Liver Involvement in Sickle Cell Trait: A Case Control Study among Nepalese Indigenous Tharu Community

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Aims: Sickle cell trait (SCT) or the carrier state for sickle cell anemia may suffer from a wide range of hepatic alterations, from asymptomatic mild liver function test abnormalities to cirrhosis and acute liver failure. A large portion of the Tharu indigenous people in Nepal have greater incidence of this carrier state, and they remain ill-understood. Therefore, aim of our current study was to evaluate the hepatic alterations among indigenous Tharu population by liver function test parameters.

Methods: A case control study was conducted among Tharu indigenous people living in Dang, mid-western region of Nepal. Thirty one suspected SCT patient and 31 healthy controls were included in the study. Fasting venous blood samples (5 ml) were subjected to complete blood count (CBC), hemoglobin electrophoresis and liver function test profile. SCT were confirmed by CBC finding & hemoglobin electrophoresis pattern. Student t test was applied for comparison between two groups at 95% CI using SPSS 16.0 version.

Results: Serum total bilirubin (0.87±0.15 vs 0.69±0.26) and indirect bilirubin (0.64±0.18 vs 0.49±0.22) were significantly higher among SCT compared to control while serum direct bilirubin (0.22±0.08 vs 0.18±0.08) was not significant (p =0.161). Likewise, serum total protein (7.64±0.67 vs 7.25±0.53) was significantly higher among SCT though there was no significant difference (p=0.085) in the mean values of albumin (4.13±0.49 vs 4.31±0.31). Furthermore, Serum aspartate transaminase (AST) and alanine transaminase (ALT) was significantly higher among SCT group with mean value of (61.06±28.67 vs 28.97±6.29) and (62.94±41.07 vs 32.03±6.34) respectively.

Conclusions: The case report documents the possibility that patients with sickle cell trait (SCT) might have mild liver abnormalities. We anticipate that comprehensive blood testing including liver function profile test in diagnostic algorithm of SCT might manifest early diagnosis and causes of liver disease.

Keywords: Liver function test, Indigenous Tharu community, Sickle cell trait

PE - 015

The Association between Tumor Necrosis Factor-alpha Polymorphism (-308, G/A) and Acute Solid Organ Rejection

Min-Su Park

University School of Medicine

Aims: Currently, the association between tumor necrosis factor-alpha (TNF-α) gene polymorphisms and the risk of acute rejection (AR) of a solid organ allograft is unclear. Therefore, we performed a meta-analysis to investigate this association.

Methods: Forty-five case-control studies were included in this meta-analysis. The pooled p-value, OR and 95% CI were used to measure the strength of the association.

Results: The A allele and genotypes including the A allele were significantly associated with AR susceptibility in solid organ recipients (A allele vs. G allele, random model, OR= 1.379, 95% CI =1.082-1.759, p = 0.009; A/A+A/G genotypes vs. G/G genotype, random model,

OR = 1.413, 95% CI = 1.077-1.854, p = 0.013; A/A genotype vs. A/G+G/G genotypes, fixed model, OR = 1.516, 95% CI = 1.032-2.227, p = 0.034, respectively). The A/A genotype was associated with AR risk in liver transplantation recipients (fixed model, OR = 2.975, 95% CI = 1.322-6.693, p = 0.008). Combined genotypes (A/A genotype + A/G genotype) contributed to AR susceptibility in renal allografts (OR = 1.406, 95% CI = 1.050-1.882, p = 0.022).

Conclusions: This meta-analysis found that one particular TNF-α polymorphism (−308, G/A) may increase the risk for acute rejection. In the future, larger studies are needed to substantiate these findings.

Keywords: Transplantation, Acute rejection, Polymorphism

PE - 016

Whole-genome Sequencing of Two Liver Tumors from One Patient

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Department of Internal Medicine, Korea University College of Medicine[1], Department of Surgery, Korea University College of Medicine[2], Department of Pathology, Korea University College of Medicine[3]

Aims: There is widely known that numerous genomic variance involved in carcinogenesis. Recent advances in technology make it possible to approach to them closer. The aim of this study is to elicit critical genomic variance in different liver cancer.

Methods: We sequenced short-insert (150bp, on average) genomic libraries of two primary multicentric liver tumors and one non-cancerous liver (NCL) tissue surgically resected from a male with chronic hepatitis B. The HiSeq X-Ten sequencer was used with 150-bp paired-end reads. Among two liver tumors, one was combined hepatocellular-cholangiocarcinoma (CHCCC) and the other was well differentiated hepatocellular carcinoma (HCC). After alignment to human reference genome and removal of duplications, three genomes were compared with each other.

Results: We obtained nucleotide sequences covering 106.0 Gb of CHCCC genome (37.1 x coverage), 102.6 Gb of HCC genome (35.9 x coverage), and 106.5 Gb (37.3 x coverage) of NCL genome. The sequenced reads covered 99.5% on all three genomes. Comparison of the CHCCC and NCL genomes showed 13,544 somatic single nucleotide variants (SNV), 3,789 small insertions and deletions, and 57 structural variants in CHCCC genome. Distinct SNVs were composed of 2.2% on exon, 37.3% on intron, and 60.5% on intergenic regions. Comparison of the HCC and NCL genomes showed 3,675 somatic single nucleotide variants (SNV), 3,491 small insertions and deletions, and 18 structural variants in HCC genome. Distinct SNVs in HCC were composed of 2.6% on exon, 39.9% on intron, and 57.5% on intergenic regions.

Conclusions: The prevalence of somatic SNVs and structural variants in CHCCC is much more than HCC when compared with NCL. And that indicates that more complex process involved in CHCCC. Further researches will be performed for finding significant changes and process, and validation.

Keywords: Combined hepatocellular cholangiocarcinoma, Hepatocellular carcinoma, Whole genome sequencing

HBV, Basic

PE - 017

Suppression of Interferon-mediated Anti-HBV Response by a Single CpG Methylation in 5'UTR of TRIM22

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Background & Aims: Interferons (IFNs) mediate direct antiviral activity. It plays a crucial role in early host immune response against viral infections. However, IFN therapy for hepatitis B virus (HBV) infection is known to be less effective than in other viral infections.

Methods: We explored the cellular targets of HBV in response to IFNs using proteome-wide screening.

Results: We identified the down- or up-regulated proteins in model cells after the IFN treatment using LC-MS/MS. We found the several downregulated IFN-stimulated genes (ISGs) including TRIM22 known as an antiviral protein against retroviruses. We demonstrated that HBx suppresses the transcription of TRIM22 through a single CpG methylation at its 5'UTR, which further reduces the IRF1 binding affinity thereby suppressing the IFNs-stimulated induction of TRIM22.

Conclusion: Our findings were verified using a mouse model and primary human hepatocytes (PHHs) and may provide a mechanism how HBV evade host innate immune system.

Keywords: Interferons, Hepatitis B virus, TRIM22, Single CpG methylation

PE - 018

Hepatitis B Virus Enhances Promoter Activity of Alpha-fetoprotein in Cytokine-dependent Manner

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Aims: Alpha-feotoprotein (AFP) is one of the most widely used biomarker for hepatocellular carcinoma(HCC). However, AFP frequently elevates in chronic hepatitis without evidence of HCC. We postulated that HBV per se may transcriptionally activate expression of AFP .

Methods: Human AFP promoter and enhancer sequence was cloned into PGL3-Basic Vector. Luciferase assay was performed to assess the AFP promoter activity in various conditions simulating chronic HBV infection.

Results: Tranasfection with 1.1x genome HBV significantly activated AFP promoter activity. Individual protein expression (HBsAg, HBcAg, HBxAg) did not affect the promoter activity, indicating full genome

HBV may directly and/or indirectlly act on the promoter, Treatment with inflammatory cytokines (TNAa and IFNr) additionally increasese promoter activity.
Conclusions: HBV replication induces transcriptional activation of AFP promoter. Cytokines in immune clearance phase may augment AFP promoter activity.
Keywords: Hepatitis B virus, Alpha-fetoprotein, Promoter

PE - 019

Marked Decreases of Foxp3 and CTLA-4 Are Associated with Strong Antiviral Effects of Tenofovir in Patients with Chronic Hepatitis B

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Aims: Immune regulatory molecules such as forkhead box P3 (Foxp3) on CD4+ T cell and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) on CD8+ T cell are associated with antiviral effector T cell dysfunction, which influences on T cell exhaustion and persistent viral infection in patients with chronic hepatitis B. These Foxp3 and CTLA-4 are up-regulated in chronic hepatitis B. During antiviral therapy with tenofovir, the expressions of Foxp3 and CTLA-4 could be changed. We investigated the relationship between antiviral effects of tenofovir and the expression of Foxp3 and CTLA-4 during tenofovir treatment in chronic hepatitis B.
Methods: Eight patients with chronic hepatitis B under tenofovir treatment were enrolled for detection of Foxp3 on CD4+ T cell and CTLA-4 on CD8+ T cell. Peripheral blood mononuclear cells were isolated from these subjects before tenofovir treatment (T0), 3 month (T3) and 6 month (T6) during tenofovir treatment. For antiviral effect analysis, serum HBV DNA levels were checked at same time. The expressions of Foxp3 and CTLA-4 on T cells were monitored by flow cytometry.
Results: Three patients (3 of 8) showed marked decreases of Foxp3 and CTLA-4 during tenofovir therapy (group 1). Five patients (5 of 8) showed minimal changes of Foxp3 or CTLA-4 during tenofovir therapy (group 2). Group 1 showed complete virologic response within 6 month therapy regardless of baseline HBV DNA level but, group 2 showed complete virologic response within 6 month therapy only in patients with low baseline HBV DNA level (< 7log HBV DNA).
Conclusions: Among the patients with chronic hepatitis B, the patients who showed marked decrease of Foxp3 and CTLA-4 during tenofovir therapy are associated with strong antiviral effects of tenofovir regardless of baseline HBV DNA level. This finding suggests that restoration of HBV-specific T cell strengthens the antiviral effects of tenofovir.
Keywords: Foxp3, CTLA-4, Tenofovir, Chronic hepatitis B

PE - 020

Foxp3 and PD-1 Except CTLA-4 Are Decreased Significantly during 1 Year Tenofovir Therapy in Chronic Hepatitis B

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Aims: Immune regulatory molecules such as forkhead box P3 (Foxp3) on CD4+ T cell and programmed death-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) on CD8+ T cell are associated with antiviral effector T cell dysfunction, which influences on T cell exhaustion and persistent viral infection in patients with chronic hepatitis C and chronic hepatitis B, These Foxp3, PD-1 and CTLA-4 are up-regulated in chronic viral infection such as chronic hepatitis C, chronic hepatitis B and human immunodeficiency virus infection but there is few report about the role of Foxp3, PD-1 and CTLA-4 in patients with chronic hepatitis B during antiviral therapy with tenofovir. We investigated the expression of Foxp3, PD-1 and CTLA-4 during 1 year tenofovir treatment in patients with chronic hepatitis B.
Methods: Thirty patients with chronic hepatitis B under tenofovir treatment were enrolled for detection of Foxp3, PD-1 and CTLA-4 on T cells. Peripheral blood mononuclear cells (PBMC) were isolated from these subjects before tenofovir treatment (T0), 1 month (T1), 3 month (T3), 6 month (T6) and 12 month (T12) during tenofovir treatment. The expressions of Foxp3, PD-1 and CTLA-4 on T cells were monitored by flow cytometry.
Results: T cells from patients with chronic hepatitis B under tenofovir treatment showed decreased expression of Foxp3 and PD-1 at T12 compared to T0 significantly but, the expression of CTLA-4 were decreased initially then increased at T12 compared to T0.
Conclusions: In chronic hepatitis B, PD-1 as inhibitory T cell molecules and FoxP3 as regulatory T cell marker are down-regulated during 1 year tenofovir therapy, which could restore HBV-specific T cell function during tenofovir antiviral therapy. Interestingly, CTLA-4 may be up-regulated during 12 months tenofovir therapy in chronic hepatitis B, may play an important role in failing to eradicate HBV in spite of complete virologic response with tenofovir.
Keywords: CTLA-4, Tenofovir, Chronic hepatitis B

HBV, Clinical

PE - 021

Clinical and Virological Features in Chronic Hepatitis B Patients with Entecavir Resistance

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Aims: Treatment of chronic hepatitis B (CHB) by antiviral agents needs the permanent therapeutic period, because withdrawal of the treatment can result in virological relapse of hepatitis B virus (HBV) or hepatitis B flares. However, the long-term therapeutic period has inevitably caused the development of drug-resistance. Though en-

tecavir (ETV) with high genetic barrier is known to develop little or no drug-resistance, some cases about ETV resistance have been reported, especially among CHB patients with lamivudine (LMV) resistance. The aim of our study was to investigate clinical and virological features in CHB patients with ETV resistance.

Methods: From 2011 January to 2014 December, a total of ten patients with amino acid substitutions at HBV rtT184F/I/A, rtS202G, or rtM250L along with rtM204I/V mutation were enrolled. The selected subjects were investigated about the previous antiviral agent and therapeutic duration, and analyzed about clinical and virological features including response of rescue therapy retrospectively.

Results: The ratio of female to male was equal in the enrolled patients. The median age was 48.0 years. Along with rtM204V/I mutants, mutation of HBV rtS202G was detected in 5 patients, and mutation of HBV rtT184I/A was detected in 3 patients. In addition, mutant of HBV rtM250L or rtT184F+rtS202G was founded in single patient, respectively. Mean duration of the previous antiviral therapy was 47.7 ± 19.0 months. As antiviral therapy prior to development of ETV resistance, ETV (0.5 mg) monotherapy, LMV monotherapy, LMV-ETV (1.0 mg) sequential monotherapy, and clevudine-ETV (1.0 mg) sequential monotherapy was used in 5 patients, 2 patients, 2 patients, and 1 patient, respectively. At the time of development of ETV resistance, seropositive HBeAg was detected in nine patients, and mean serum HBV DNA was 5.0 ± 1.4 $\log_{10}$ IU/ml. ETV plus tenofovir (TDF), and TDF alone was administered in 9 patients, and 1 patient for rescue therapy of ETV resistance. Complete response was achieved in 7 patients, and partial response was achieved in 3 patients.

Conclusions: This study showed that comparable virological response was achieved by ETV plus TDF and TDF monotherapy, and ETV resistance was developed in CHB patients with ETV monotherapy as well as LMV resistance.

Keywords: Chronic hepatitis B, Entecavir, Resistance, Tenofovir

PE - 022

HBsAg Level Change in Chronic Hepatitis B Patients Who Achieved Virological Response with Oral Antiviral Agents

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Aims: Oral antiviral agents are main stay of chronic hepatitis B (CHB) treatment and most patients can achieve virological response (VR, undetectable HBV DNA). However, final end point is HBsAg loss and seroconversion. We aimed to evaluate HBsAg level change in CHB patients who achived VR with oral antiviral agents.

Methods: This is a retrospective study and the treatment naive CHB patients who achived VR with oral antiviral agents in Konkuk university hospital more than 3 years were enrolled. HBsAg level change was analyzed with Friedman test.

Results: Total 105 patients were included in this study. Median age was 51 years and 33 patients were male (31.4%). HBeAg positive patients were 60 (57.1%), cirrhosis patients were 45 (42.9%) and hepatocellular carcinoma patients were 15 (14.3%). Used agents were lamivudine (LMV) in 45 patients (42.9%), entecavir (ETV) in 45 patients (42.9%) and tenofovir (TDF) in 15 patients (14.3%). During 3 years teatment, HBsAg level was reduced from mean 3.24 (log10 IU/mL) to 3.11 (log10 IU/mL) significantly (p=0.005). In subanalysis according to HBeAg status and agents, only ETV treated patients showed significant HBsAg reduction (p=0.001). During 5 years treatment except TDF treated patients due to short duration, HBeAg negative (p<0.001), LMV treated (p=0.001), ETV treated (p=0.038) patients showed significant HBsAg reduction.

Conclusions: Successful oral antiviral agents treatment can lead to HBsAg reduction in CHB patients. More powerful agent may reduce HBsAg more rapidly especially in HBeAg negative patients.

Keywords: HBsAg, Chronic hepatitis B, Antiviral agent

PE - 023

Clinical, Biochemical and Virological Differentiation in Acute Hepatitis B and Chronic Hepatitis B with Acute Exacerbation

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Aims: Many areas of the world including Korea, China and Taiwan are known as endemic areas for hepatitis B virus infection. In these countries, it is difficult to distinguish acute hepatitis B (AHB) from chronic hepatitis B with acute exacerbation (CHB-AE) due to the similar serological profiles and clinical features. Distinction between AHB and CHB-AE is clinically important to decide the therapeutic strategy including the initiation of antiviral therapy. The aim of this study was to investigate clinical, biochemical and virological differentiation in patients with AHB and CHB-AE.

Methods: A total of fifty-nine patients with immunoglobulin M antibody to hepatitis B core antigen seropositivity from January 2005 to December 2014 were enrolled. The subjects were divided into the AHB group (n=40) and the CHB-AE group (n=19) according to previous history of hepatitis B infection or results of radiologic examination through review of medical records. Clinical, biochemical and virological features were analyzed and compared between the both groups retrospectively.

Results: Presence of jaundice and hepatitis B envelop antibody (HBeAb) seropositivity in the AHB group were significantly higher than those in the CHB-AE group (72.5% vs. 42.1%; p=0.042 and 60.0% vs. 26.3%; p=0.002, respectively). Levels of serum HBV DNA significantly differed between the AHB group and the CHB-AE group (4.9 $\log_{10}$IU/ml vs. 6.7 $\log_{10}$IU/ml; p=0.000). In addition, levels of serum alpha-fetoprotein significantly differed in the two groups (5.5 ng/ml vs. 135.5 ng/ml; p=0.001). However, no significant difference in seropositivity rates of hepatitis B surface antigen and hepatitis B envelop antigen was observed between the both groups (90.0% vs. 100%; p=0.294 and 55.0% vs. 78.9%; p=0.133, respectively). In addition, levels of hepatitis B surface antigen (ratio of the optical density of the sample to the cut-off value [S/CO] <20) was not significantly different from the AHB group and CHB-AE group (2041.2 vs. 2078.6; p=0.756).

Conclusions: Our study showed that the presence of jaundice and HBeAb seropositivity as well as the levels of serum HBV DNA and

alpha-fetoprotein might be used to distinguish between patients with AHB and patients with CHB-AE.

Keywords: Hepatitis B virus, Acute hepatitis B, Chronic hepatitis B, Acute exacerbation

PE - 024

Treatment Modification Is not Needed for Early Alanine Aminotrasferase Flare in Treatment-naïve Patients with Chronic Hepatitis B Initiated on Tenofovir

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Aims: Tenofovir disoproxil fumarate (TDF) is a potent antiviral drug used in the treatment of patients with chronic hepatitis B (CHB). The aim of this study was to evaluate the antiviral efficacy and safety of continuous TDF monotherapy after early alanine aminotrasferase (ALT) flare in treatment-naïve patients initiated on TDF.

Methods: A total of 40 treatment-naïve CHB patients were treated with a 300-mg once-daily dose of TDF for more than 12 weeks. Virological markers of hepatitis B virus (HBV) and biochemical data were monitored at baseline and every 1-3 months during the therapy. The proportion of patients with undetectable HBV DNA level (< 1.25 $\log_{10}$ IU/ml) was noted.

Results: At the baseline, median age was 44 years, and there were 31 male subjects, and 33 HBeAg-positive subjects; there was no cases of cirrhosis. Median follow-up was 36 weeks (12-140 weeks). Baseline mean HBV DNA levels were 6.04 ± 2.3 $\log_{10}$ IU/mL. Baseline mean ALT levels were 157 ± 144 IU/mL. Serum HBV DNA was undetectable in 58.3% and 100% of the patients at weeks 48 and 96. HBeAg loss was observed in 2 patients during the treatment period. Two HBeAg-positive patients (5%) showed ALT flares (>10 × upper limit of the normal range), without viral breakthrough, HBeAg loss, or seroconversion within first 4 weeks after the start of TDF monotherapy. ALT flares resolved within 4 weeks and both patients showed virologic response without interruption or discontinuation of treatment. Among baseline factors, young age (≤ 40 years) was predictive of early ALT flare (p = 0.048).

Conclusions: Continuous TDF monotherapy may be effective and safe in treatment-naive patients with CHB experiencing early ALT flares without viral breakthrough. Early ALT flares may be related to young age in treatment-naïve patients with CHB started on TDF.

Keywords: Alanine aminotransferase, Tenofovir, Chronic hepatitis B

PE - 025

Insulin Resistance Increases Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients

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Aims: To date, few data is available whether insulin resistance (IR) increases hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B virus (HBV) infection.

Methods: This retrospective cohort included 2,119 chronic HBV infected individuals [age: 50.2 ± 7.7, male = 1,266 (59.7%), diabetes = 149 (7.0%), obesity ≥ 25 kg/m2 = 722 (34.0%)] who participated in a regular health screening exam that included fasting blood glucose and C-peptide levels between 2004 and 2013. IR was estimated with homeostasis model assessment index (HOMA2-IR) using C-peptide and fasting blood glucose levels. Association between IR and development of HCC were assessed.

Results: During a median of 5.1 years of follow-up (min-max: 1.0 - 10.5 years), 57 patients (2.7%) developed HCC. The 5-year cumulative incidence rate of HCC gradually increased with the increase of HOMA2-IR [0.6%, 1.4%, 3.7% and 4.0% for 1st (<0.93), 2nd (0.93-1.25), 3rd (1.25-1.68) and 4th (≥1.68) quartile of HOMA2-IR, p = 0.009]. HCC risk was higher when HOMA-IR was ≥ 1.2 [hazard ratio (95% CI): 2.02 (1.07-3.79), p = 0.029, adjusted for age, sex, aspartate aminotransferase to platelet ration index, HBV DNA levels and antiviral therapy]. The HCC incidence rate was constantly higher when HOMA-IR was ≥ 1.2 compared to patients with HOMA-IR < 1.2 for all-clinically relevant subgroups analyzed.

Conclusions: The IR was associated with the development of HCC, indicating that IR may contribute to the hepatocarcinogenesis in chronic HBV infected patients. Assessing IR can be helpful for stratifying individual risk for HCC.

Keywords: Liver cancer, Insulin resistance, Metabolic syndrome, Hepatitis B virus

PE - 026

Histological and Clinical Features of Chronic Hepatitis B Patients with Persistent Viral Load and Normal or Slightly Elevated Serum Alanine Aminotransferase Levels

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Aims: Administration of antiviral therapy is largely dependent on hepatitis B virus (HBV) DNA titer and serum alanine aminotransferase (ALT) levels in patients with chronic hepatitis B in South Korea because of limited reimbursement policy. However, there is a lack of correlation between necroinflammatory activity and the degree of increase in ALT levels. We evaluated the histologic findings in chronic hepatitis B (CHB) patients with high serum HBV DNA levels and normal or slightly elevated serum ALT levels.

Methods: Ninety-two patients with HBV DNA ≥1,000 copies/mL and aspartate aminotransferase (AST) or ALT <80 IU/L for >6 months who had undergone ultrasonography-guided liver parenchymal biopsy at a single institution between January 2001 and February 2016 were enrolled and retrospectively evaluated. Histological grading of chronic hepatitis was determined according to the standardized guide-

line proposed by the Korean Study Group for the Pathology of Digestive Diseases.

Results: Among 92 patients with CHB (median age 50 years, male 51.1%), stage 2-4 fibrosis and grade 3-4 lobular or porto-periportal activity was observed in 40 (43.5%) and 35 (38.0%) patients, respectively. Nucleos(t)ide analogues (NA) were prescribed without coverage of National Health Insurance in 74 patients (38 of 40 patients with grade 2-4 fibrosis and all 35 patients with grade 3-4 lobular or porto-periportal activity) for a median duration of 62.5 months (range: 2-132 months). At baseline, liver cirrhosis was confirmed in 21 of 74 patients in the NA-treated group and 2 of 18 patients in the observation group, respectively. During a median follow-up duration of 69 months (range: 0-132 months), liver cirrhosis and hepatocellular carcinoma developed in 1 patient and 4 patients of the NA-treated group, respectively. The median follow-up duration of the observation group was 19.5 months (range: 1-72 months), and the development of cirrhosis or hepatocellular carcinoma was not identified.

Conclusions: A substantial proportion of CHB patients with persistent viral load and persistently normal or slightly elevated AST or ALT underwent antiviral treatment due to significant histologic features on liver biopsy.

Keywords: Chronic hepatitis B, Liver histology, HBV DNA, Alanine aminotransferase

PE - 027

Long-term Efficacy of Tenofovir-based Rescue Therapy in Prior Lamivudine Resistant Chronic Hepatitis B Patients with Failure to Lamivudine and Adefovir Combination Therapy

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Aims: In chronic hepatitis B (CHB) patients, lamivudine (LAM) and adefovir (ADV) combination therapy is commonly used as a rescue therapy for LAM resistance, but it often results in incomplete viral suppression. Tenofovir (TDF) alone or in combination with entecavir (ETV) or LAM has been recommended as a rescue strategy for patients with suboptimal responses during LAM and ADV combination therapy.

Methods: We evaluated the long-term efficacy of TDF-based rescue therapy in 90 LAM-resistant CHB patients who failed to respond to LAM plus ADV rescue therapy. We also investigated the efficacy of TDF monotherpy versus TDF/LAM combination therapy, types of pre-existing ADV mutation.

Results: Resistance to ADV (ADV-R) was present in 51 patients (56.7%); rtA181T/V, rtN236T and rtA181T/V +rtN236T in 29, 3 and 19 patients, respectively, and the remaining 39 patients (43.3%) had a partial virologic response to LAM/ADV combination (ADV-P). The study subjects were treated with TDF alone (n=23) or TDF/LAM combination (n=67). Virologic response (VR) was achieved in 78 patients (86.7%). The cumulative probabilities of achieving VR were 65.6%, 76.9%, 85.4%, and 89.3% at 6, 12, 24, and 36 months, respectively. HBeAg seroclearance occurred in 6 (12.5%). ALT levels were normalized in 69 (94.5%) of 73 patients with elevated ALT at baseline. A higher proportion of patients in the ADV-P group achieved a VR at 12 months (89.7% vs. 66.7 %) and 24 months (97.4% vs. 75.8%) than that of patients in the ADV-R group (log-rank test, P<0.001). The rates of VR were not significantly different between TDF monotherapy and TDF/LAM combination therapy groups. Treatment efficacy of TDF alone or TDF/LAM combination was not statistically different according to pre-existing ADV or LAM resistant strains. In multivariate analysis, absolute HBV DNA levels at the start of TDF rescue treatment (P<0.001; OR, 0.556; 95% CI, 0.445-0.695) were the only significantly associated with VR.

Conclusions: Long-term efficacy of TDF-based therapy was effective in maintaining viral suppression in patients with LAM-resistant patients who failed to respond to LAM/ADV combination therapy. TDF monotherapy was as effective as TDF/LAM or TDF/ETV combination therapy. Therefore, TDF mono-rescue therapy is an appropriate treatment in these patients.

Keywords: Tenofovir, Lamivudine resistance, Adefovir resistance, Chronic hepatitis B

PE - 028

Comparison of Efficacy between Tenofovir Disoproxil Fumarate and Entecavir in Chronic Hepatitis B Patients with High Hepatitis B Virus DNA

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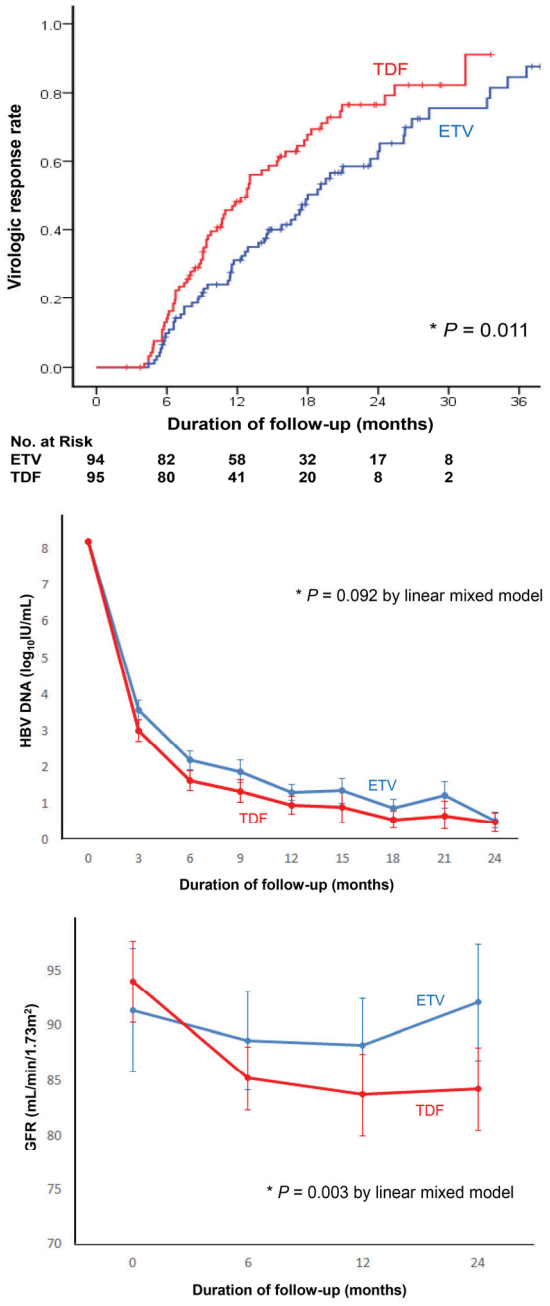
Aims: High Hepatitis B Virus (HBV) DNA is associated with increased risk of cirrhosis and hepatocellular carcinoma in chronic hepatitis B patients. There are few studies comparing the efficacy of tenofovir disoproxil fumarate (TDF) and entecavir (ETV) in patients with high HBV DNA. This study aimed to evaluate the efficacy of TDF and ETV in chronic hepatitis B patients with high HBV DNA.

Methods: We conducted a retrospective analysis of data from 189 consecutive chronic hepatitis B patients with high HBV DNA titers (≥10(8) IU/mL). We included nucleos(t)ide analogue (NA) treatment-naïve patients or NA-experienced patients without detectable genotypic resistance. 95 patients were treated with TDF and 94 were treated with ETV. Complete virologic response (CVR) rate in two groups was analyzed by Kaplan-Meier curve analysis and Cox proportional hazards model.

Results: The median duration of follow-up was 15.5 months. The median time to CVR was 12.8 and 18.0 months in TDF group and ETV group, respectively (P=0.011 by log-rank test). In multivariate analysis, TDF group had significantly higher probability of CVR (hazard ratio [HR]=1.72, 95% confidence interval [CI]=1.16-2.56; P=0.007) after adjustment for age, HBeAg status, aminotransferase and previous NA experience. The cumulative probability of HBeAg loss was not significantly different between two groups (P=0.210 by log-rank



test). None of the patients had discontinued medication due to adverse reactions and GFR at each time point was significantly different in two groups (P=0.003 by linear mixed model).

Conclusions: Tenofovir disoproxil fumarate is superior to entecavir in achieving complete virologic response in chronic hepatitis B patients with HBV DNA greater than 10(8) IU/mL.

Keywords: Tenofovir, Entecavir, High HBV DNA, Efficacy

PE - 029

Prolonged Tenofovir Monotherapy for Partial Virologic Response to Tenofovir in Treatment-naive Chronic Hepatitis B Patients

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Aims: Tenofovir disoproxil fumarate (TDF) has highly potent antiviral activity with a high genetic barrier to resistance in chronic hepatitis B (CHB) patients. The optimal management of CHB patients exhibiting a partial virologic response (PVR) to TDF is currently not established. The aim of this study was to evaluate the long-term efficacy of prolonged TDF monotherapy in treatment-naïve CHB patients exhibiting a PVR to TDF therapy.

Methods: This retrospective study included 139 treatment-naïve CHB patients treated with TDF for ≥48 weeks and who received continuous TDF monotherapy for ≥24 weeks at Daegu Catholic University Hospital. PVR was defined as a decrease in serum HBV DNA of more than 2 log10 IU/mL from baseline but detectable HBV DNA by real-time PCR assay at week 48. All patients were monitored at baseline and every 3 months during treatment.

Results: Thirty of 139 patients (21.6%) showed PVR. The mean follow-up duration in PVR group was 90.0±17.7 weeks. The mean age was 48.4±13.9 years, and 20 patients (66.7%) were men. Twenty-two patients (73.3%) were HBeAg-positive, and 13 patients (43.3%) had cirrhosis. Fifteen of 30 patients (50.0%) achieved a virologic response (VR, HBV DNA <20 IU/ml) during prolonged TDF monotherapy for ≥24 weeks. VR rate in HBeAg-positive patients was 50.0% (11/22). Among 15 patients who did not achieve a VR during continuous TDF therapy, 10 patients had poor drug compliance. The overall cumulative rates of VR at week 60, 72, 84, and 96 from treatment initiation in patients with PVR were 25.0%, 41.4%, 47.1%, and 53.3%, respectively. The PVR was associated with HBV DNA levels at baseline, week 4, 12, and 24, and also with virologic breakthrough.

Conclusions: Long-term continuous TDF monotherapy with good medication compliance may be effective for achieving VR in treatment-naïve CHB patients exhibiting a PVR to TDF therapy.

Keywords: Chronic hepatitis B, Tenofovir, Partial virologic response

PE - 030

Relevance of Baseline Hepatitis B Surface Antigen Levels and Hepatitis B Virus DNA Levels for Predicting Treatment Response during Tenofovir Therapy in Chronic Hepatitis B Patients

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Aims: The aim of this study was to analyze the baseline serum quantitative hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA levels in chronic hepatitis B (CHB) patients for predicting the virologic treatment response during tenofovir (TDF) therapy.

Methods: 49 ethnically homogenous genotype C CHB patients who received to tenofovir for 48 weeks were enrolled. Serum levels of HBsAg and HBV DNA were assessed at baseline, 12 weeks, 24 weeks and 48 weeks of TDF therapy. Virologic treatment response (VTR)

was defined as serum HBV DNA undetectability (< 30 IU/mL) after TDF administration. All patients underwent routine biochemical test including liver function.

Results: Among 49 CHB patients (55% male, median age 44.5yr), 27 (55%) were HBeAg positive. Mean baseline HBsAg level and HBV DNA level were 3.47 ± 0.71 log10IU/mL and 6.37 ±1.36 log10IU/mL, respectively. In HBeAg positive patients, baseline HBV DNA level was correlated with treatment response at 12 weeks (p=0.004) and 24 weeks (p=0.005) of TDF therapy. Also, patients with baseline serum HBsAg ≤ 4 log10IU/mL showed significantly high VTR at 24 week TDF therapy (p=0.05). In HBeAg negative patients, baseline HBV DNA level was correlated with VTR at 12 weeks TDF therapy. In this group, however, baseline HBsAg titers were not correlated with VTR.

On the evaluation of VTR in all enrolled patients at 12, 24 and 48 weeks after TDF therapy, patients with complete VTR at week 12, 24 and 48 after TDF therapy showed significantly low baseline HBV DNA levels compared to those with no VTR (p<0.05). For the baseline HBsAg levels, patients with VTR at week 12, 24 and 48 after TDF therapy showed significantly low baseline HBsAg levels as well (p<0.05). Also, VTR at week 24 and 48 after TDF therapy were significantly low in patients with HBeAg positive. And, the baseline liver stiffness using fibroscan showed no significant correlations with VTR after TDF therapy.

Conclusions: We suggest that baseline quantitative HBsAg and HBV DNA level could correlate with the virologic treatment response during TDF therapy. Also, further study to find the correlation between HBsAg kinetics and other treatment response like HBeAg seroconvirsion on long term TDF therapy will be needed.

Keywords: Hepatitis B surface antigen quantification, Hepatitis B virus DNA, Tenofovir

PE - 031

Development of Hepatocellular Carcinoma after Hepatitis B Surface Antigen Seroclearance in Chronic Hepatitis B

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Aims: Recent studies have found that hepatocelluar carcinoma (HCC) can still develop in chronic hepatitis B patients after hepatic B surface antigen (HBsAg) seroclearance. The aim of this study was to assess the incidence of HCC and the risk factor for the development of HCC after HBsAg seroclearance.

Methods: This is a retrospective observational study of 87 patients with HBsAg seroclearance followed between January 1981 and March 2016. Incidence of HCC after HBsAg seroclearance and associated factors for the development of HCC were evaluated. These patients continued to undergo HCC surveillance that included test for α -fetoprotein levels, abdominal ultrasonography or abdominal computed tomography.

Results: The median follow-up period from HBsAg seroclearance was 37 months (range, 1 to 168 months). The mean age at HBsAg seroclearance was 51.9 years. At the time of HBsAg seroclearance, 6 patients (6.9%) had detectable hepatitis B virus DNA and 28 (32.2%) had cirrhosis. During the follow up, HCC was developed in 6 of 87 patients (6.9%). The only associating factor for development of HCC was the presence of liver cirrhosis at the time of HBsAg seroclearance (p=0.026). There was no significant differences in age at the time of HBsAg seroclearance between patients with and without HCC (p=0.559).

Conclusions: HCC can develop after HBsAg seroclearance in patients with especially in those with the presence of liver cirrhosis at the time of HBsAg seroclearance. Thus, HCC surveillance should be carried out for patients who achieved HBsAg seroclearance in the same manner as for the patients with HBsAg positive.

Keywords: HBsAg seroclearance, Hepatocellular carcinoma, Liver cirrhosis

PE - 032

Efficacy of Antiviral Treatment in Chronic Hepatitis B with Chronic Kidney Disease

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Aims: The treatment of chronic hepatitis B in patients with chronic kidney disease is complex and the information is scarce. The treatment in this population is based on nucleoside or nucleotide analogue and their dosage should be adjusted with creatinine clearance. The aim of this study was to assess the efficacy of antiviral therapy in this population.

Methods: The medical records of twenty chronic hepatitis B patients with chronic kidney disease who had undergone dosage adjustment of antiviral agent according to renal function from March 2006 through March 2016. The virologic response showed a decrease in a value of less than 20IU/mL of HBV DNA and biochemical response showed a decrease in a value of less than 40IU/mL of serum ALT.

Results: Five, eight, seven patients were treated with lamivudine, entecavir, tenofovir respectively. After 48 weeks one patient(20%) with lamivudine, three patients(37%) with entecavir, five patients(71%) with tenofovir showed a virologic response. All patients except one patient with entecavir and one patient with tenofovir experienced biochemical response after 48 weeks.

Conclusions: In this study tenofovir showed good therapeutic effect in chronic hepatitis B with chronic kidney disease who had undergone dosage adjustment of antiviral agent according to renal function. But more larger prospective studies are needed.

Keywords: Chronic hepatitis B, Chronic kidney disease, Treatment efficacy

PE - 033

Comparison of the Efficacy of Entecavir and Tenofovir Monotherapy for the Treatment of Treatment-naïve Patients with Hepatitis B Virus in Korea

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Aims: Current treatment guidelines recommend either entecavir (ETV) or tenofovir (TDF) as first line treatment for management of chronic hepatitis B patients given their high antiviral potency, favorable tolerability profile, and high genetic barriers to the development of antiviral resistance. However, it is not clear whether the efficacy reported from head-to-head trial is similar to the outcomes seen in routine practice. So, our aim is to investigate the treatment outcomes of antiviral therapy in a clinical practice.

Methods: We conducted a prospective cohort study of 130 treatment-naïve patients who started either ETV or TDF by randomization manner between Januanry 2013 and December 2014. Primary endpoint was complete viral suppression rate (HBV DNA real-time PCR < 20 IU/mL) at 12 month after treatment (ClinicalTrials.gov Identifier: NCT01776814).

Results: Total 130 CHB patients were enrolled and randomized in both group. However, 15 patients were dropped by any lesion and 104 patients (80%) were remain at 12 months. The majority of patients in both ETV and TDF group were male (73%), HBeAg negative (60%), and non-cirrhotic patients (52%). Pretreatment serum ALT, HBV DNA level, bilirubin, and albumin level were similar between two groups (p=n.s.). At treatment 12 months, both group achieved similar complete virological response: 85% vs. 86%, respectively (p=0.26). Biochemical response is also similar: 95% vs. 96%, respectively (p=0.3). Among HBeAg positive patients, 6 patients showed HBeAg loss (2 patients in ETV, 4 in TDF) and 2 patients achieved HBeAg seroconversion (1 at ETV, 1 at TDF). 3 patients experienced side effect and stopped medication (1 at ETV, 2 at TDF). However, there was no serious side effect during treatment period.

Conclusions: Treatment-naïve CHB patients treated with either ETV or TDF achieved a similar rate of complete virological and biochemical response at 12 months. However, drop rate was slightly high regardless of drug and attention to medication adherence is needed in a clinical practice.

Keywords: Hepatitis B virus, Entecavir, Tenofovir, Randomization

PE - 034

The Risk of Hepatocellular Carcinoma Development in Patients with Chronic Hepatitis B Who Achieved Virological Response through Oral Antiviral Therapy versus Those in Inactive Phase

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Aims: It is not well known whether the risk of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB) treated with oral antiviral agents is similar to that of patients in inactive stage CHB. We compared the risk of HCC development between patients with CHB receiving oral antiviral therapy and those in inactive stage CHB, after adjusting for fibrotic burden.

Methods: A total of 1708 patients with CHB who achieved virological response (VR, defined as HBV-DNA <2000 IU/mL) through oral antiviral therapy (NUC-VR group) and 840 inactive carriers who had negative hepatitis B e antigen (HBeAg), normal alanine aminotransferase (ALT) level, and HBV-DNA<2000 IU/mL (IC group) were enrolled. Cumulative rate of HCC development was assessed by Kaplan-meier method with a comparison by log-rank test. Cox regression analysis was performed for multivariate analysis. Rescue therapy was performed, if appropriate.

Results: NUC-VR group had a higher portion of male (65.3% vs. 57.5%), higher total billirubin level (median 0.8 mg/dL vs. 0.7 mg/dL), lower serum albumin levels (median 4.4 g/dL vs. 4.6 g/dL), lower platelet count (median 161x103/mm3 vs. 200x103/mm3), higher proportion of ultrasonographic cirrhosis (43.8% vs. 6.3%), and higher LS value (median 7.7 kPa vs. 5.0 kPa) (all p<0.001). On multivariate analysis, NUC-VR group was at a higher risk of HCC development compared with IC group (p<0.001).

Conclusions: Even patients who achieved NUC-VR through oral antiviral therapy was at a higher risk of HCC development compared with IC group.

Keywords: Antiviral therapy, Hepatitis B virus, Inactive carrier

PE - 035

Incidence, Predictors and Clinical Course of Partial Virologic Response to Tenofovir in Treatment-naïve Patients with Chronic Hepatitis B

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Aims: Partial virological response(PVR) to nucleos(t)ide analogues are defined by patients with detectable HBV DNA by real-time PCR assay(>10-15 IU/ml) at week 48. Clinical importance of NUC PVR relates to the high risk of developing resistance to long-term HBV treatment and requires rescue therapy from potent drugs with high genetic barrier such as entecavir or tenofovir. Long -term ETV therapy is known to result in VR in treatment-naïve patients. However, clinical significance of tenofovir is not known.

We aim to assess the rates of PVR to tenofovir, the predictive factors associated with PVR, and clinical course in treatment-naïve patients with chronic hepatitis B.

Methods: Between November 2012 and December 2014, total of 519 treatment naïve patients with CHB received first-line tenofovir at Severance Hospital. The primary endpoint was the proportion of patients showing a partial virological response (PVR) during treatment. Multivariate analysis was done to evaluate predictive factors independently associated with the time to PVR. Patients with decompensated liver cirrhosis or HCC or organ transplantation prior to the TDF treatment were excluded.

Results: Among 519 patients with tenofovir therapy, virological response was achieved in 400 patients(77%) at 24 weeks of TDF therapy. Upon 48weeks of therapy, 119(22.9%) patients achieved PVR and 45(37.8%) patients achieved VR among PVR patients, following 96weeks of therapy. HBeAg positive patients achieved more PVR(119, 43.59%) compared with HBeAg negative patients(60, 26.4%). Patients with PVR were younger (mean±SD, 47±13 years, P=0.004), had higher baseline HBV DNA levels (6.2±2.1 log10 IU/ml, P=0.009) and showed less HBeAg positivity(54.6%, P<0.001) and less HBeAg seroconversion(32.5%, P<0.001) compared with patients without. Using multivariate analysis, platelet (Odds ratio [OR] 1.005, 95% CI 1.001-1.008, P=0.01) and baseline HBV DNA level (OR 1.172, 95% CI 1.028-1.337, P=0.018) were predictive factors for PVR.
Conclusions: Following 24weeks of TDF therapy, 400 patients(77%) achieved VR. 119(22.9%) patients showed PVR after 48weeks of TDF therapy. 96 weeks of TDF therapy results in VR of PVR patients(45, 37.8%)
Baseline HBV-PCR(log IU/ml) was higher in patients with PVR than patient without PVR and more patients with HBeAg showed PVR. Patients with PVR achieved less HBeAg seroconversion than patients without PVR. Elevated baseline platelet levels and baseline HBV DNA levels are predictive factors for PVR.
Keywords: Partial virological response, Tenofovir, Chronic hepatitis B

PE - 036

Factors Having Influence on ALT Normalization during Antiviral Treatment for Chronic Hepatitis B Patients

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Aims: The goals of the antiviral treatment include undetectable HBV DNA, ALT normalization, HBeAg loss or seroconversion, and HBsAg loss or seroconversion. HBV DNA and ALT are therefore monitored along with viral markers during the antiviral treatment, but there can be often cases where repetitive examinations are taken with HBV DNA or markers of other viruses as ALT is not normalized despite long term treatments. This study tries to determine factors in a real clinic situations that have influence on ALT normalization in antiviral treatment.
Methods: The subjects of the study were 136 outpatients who visited our hospitals because of chronic B viral hepatitis and were treated with tenofovir and followed up over 48 weeks after taking tenofovir. The medical records of the subjects were analyzed.
Results: The average age of the patients is 50.71±12.46, their log10 HBVDNA is 6.25±1.30, 57.6% of them had HBeAg positive, their liver cirrhosis (LC) identified by the abdominal ultrasonography was 43.1% (59/136), and 14.7% of them (20/136) had HCC. The HBeAg ALT normalization rate for the 48 weeks was 58.2% (79/136), and their HBV DNA loss for the 48 weeks was 87.1% (118/136). The serological factors related to the ALT normalization in the 48th week include red cell distribution width (RDW, p=0.05), albumin (p=0.038), alkaline phosphatase (ALP, p=0.048), and serum glucose (p=0.043) on the base line, and hence the albumin values the normal ALT group in the 48th week had been high before the treatment, while their pre-treatment RDW, ALP, and glucose values were lower than those in the group with abnormal ALT in the 48th week. On the other hand, the ALT normalization rate was higher in female patients than in male patients (73.8% vs 50.0%, p=0.013), and the ALT normalization rates differed depending on combined drugs with, for example, abnormal ALT values shown in all 8 patients taking antidiabetic agents (p=0.015). Depend on disease status, ALT normalization rate in that the rate was 84.8% in chronic hepatitis, 50.0% in fatty liver, 45.7% in LC, and 27.8% in HCC patients.
Conclusions: Based on the results of the study, it is possible for patients to have advanced liver diseases when their ALT normalization is not obtained after 48 week treatment. More long-term medication and close monitoring is thus necessary, and diabetes and fatty liver should be checked as they are factors obstructing ALT normalization.
Keywords: Alanine aminotransferase, Hepatitis B virus, Tenofovir

HCV, Clinical

PE - 037

Efficacy of Ledipasvir/Sofosbuvir plus Rivabirin among Patients with Decompensated Cirrhosis Who Underwent Liver Transplant during Participation in the SOLAR-1/-2 Studies

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Aims: The aim of this analysis is to evaluate outcomes in patients who underwent liver transplant after initiating treatment with ledipasvir (LDV)/sofosbuvir (SOF)+ribavirin (RBV) in the SOLAR-1 and SOLAR-2 trials.
Methods: We combined data from the SOLAR-1 and SOLAR-2 studies, in which 7 groups of patients with HCV genotype (GT) 1 or 4 were randomized to receive 12 or 24 weeks of LDV/SOF+ RBV: patients without a transplant with 1) Child-Pugh-Turcotte (CPT) B or 2) CPT C cirrhosis; or transplanted patients with 3) no cirrhosis (F0 to F3), 4) CPT A, 5) CPT B or, 6) CPT C cirrhosis, or 7) fibrosing cholestatic hepatitis.
Results: Seventeen patients underwent liver transplantation during the study. For all but one patient, this was the first liver transplant. Six were CPT B at screening (5 Group 1, 1 Group 5) and 11 were CPT C (Group 2). Median baseline MELD score was 17 (range 7-23), with the majority (11/17) having scores ≥15. Seven patients underwent transplant prior to completing their full course of treatment. All patients were HCV RNA <LLOQ at the time of liver transplant. All but one patient (94%, 16/17) maintained virologic response 12 weeks after transplant (pTVR12). All patients who achieved pTVR12 received at least 11 weeks of LDV/SOF+RBV. The one patient who did not achieve pTVR12 discontinued study drug on day 21 and underwent liver transplant the following day.
Conclusions: Few patients with decompensated cirrhosis treated in the SOLAR studies underwent liver transplantation after initiating LDV/SOF+RBV therapy. For the 17 who did undergo transplant, 94% achieved pTVR12. The data suggest that 11 weeks of treatment prior to transplantation can prevent reinfection of the graft. Future studies are needed to assess the optimal timing and length of treatment in the peri-transplant setting.
Keywords: Ledipasvir, Sofosbuvir, Transplantation

PE - 038

Ledipasvir/Sofosbuvir for 12 or 24 Weeks Is Safe and Effective in Kidney-transplant Recipients with Genotype 1 or 4 HCV Infection

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Aims: Interferon (IFN) and ribavirin (RBV) for the treatment of chronic hepatitis C (HCV) in kidney transplant recipients is complicated by the risk of the allograft rejection and poor tolerability. We evaluated the safety and efficacy of the IFN-free, RBV-free regimen of ledipasvir/sofosbuvir (LDV/SOF) in chronic genotype (GT) 1 or 4 HCV infected kidney transplant recipients.
Methods: Kidney transplant recipients with chronic GT1 or GT4 HCV infection, treatment-naïve and treatment-experienced, with or without compensated cirrhosis were randomized 1:1 at 5 sites in Europe to receive LDV/SOF (90 mg/400 mg) for 12 or 24 weeks. Randomization was stratified by HCV genotype, treatment history and presence or absence of cirrhosis. Cirrhosis was determined by liver biopsy (Metavir score = 4 or Ishak score ≥5), Fibroscan® >12.5 kPa, or Fibrotest® >0.75 and APRI >2. A pretreatment creatinine clearance <40 mL/min was an exclusionary criterion. The primary endpoint was SVR12.
Results: 114 patients were randomized and treated; median age was 53, 58% were male, 94% were white, 72% carried the non-CC IL28B allele, 91% had GT 1 infection, 69% were treatment-naïve, and 15% had compensated cirrhosis. The median eGFR was 56ml/min (range 35-135ml/min). All 92 patients with SVR4 data available achieved SVR4 including a patient discontinuing treatment at Week 4 due to an AE. SAEs were reported in 12 (11%) patients; 3 were assessed as treatment related: syncope, pulmonary embolism, and blood creatinine increased. The most frequent AEs were headache (19%), asthenia (13%), and fatigue (10%).
Conclusions: Administration of LDV/SOF for 12 or 24 weeks in patients with chronic HCV genotype 1 or 4 patients who have undergone kidney transplant was safe and highly effective with an SVR4 rate of 100%. Treatment was well-tolerated. SVR12 data for all patients will be presented.
Keywords: Ledipasvir, Sofosbuvir, Kidney-transplnatation

PE - 039

Ledipasvir/Sofosbuvir for 8 Weeks in Genotype 1 Treatment-naïve Non-cirrhotic Patients with HCV RNA < 6 Million IU/mL: Phase-3 and Real World

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Aims: The optimal duration of therapy to achieve SVR depends on multiple factors. In a post-hoc analysis of the Phase 3 ION-3 (treatment-naïve (TN), non-cirrhotic (NC) patients) 8 week of LDV/SOF data, a viral load (VL) <6M was shown to be the best predictor of SVR. Real world effectiveness (RWE) is often different from Phase III trials and there is a need to understand real-world 8 week regimens in a broader spectrum of patients.
Methods: RWE 8 week LDV/SOF data is emerging from multiple single-center and multicenter retrospective and prospective cohorts. In

Study	ION-3	TARGET	TRIO	Buggisch	GECCO	VA - Marshall	Ruane	Total (non ION3)
N/N (GT 1)	119/123	150/154	251/263	103/103	69/70	47/48	18/20	638/658
Age (mean)	52 (22-73	58* (19-84)	57 (18-84)	50 * (22-77)	52 * (44-58)	61 (32-75)	52 (35-66)	n/a
HIV/HCV	0	1/1	3/3	3/3	7/7	0	18/20	32/34
VL >6 million	0	0	8/8	0	9/9	0	0	17/17
Cirrhotics	0	6/6	0	0	3/3	0	0	9/9
GT 4	0	0	0	2/2	0	0	0	2/2
Tx Exp	0	8/8	0	1/1	12/12	5/5	0	26/26
SVR12 (%)	97%	97%	95%	100%	99%	98%	90%	97%

*Median age used

this analysis, the phase-3 ION-3 data is compared with data from several diverse real world populations and one post-marketing investigator sponsored HIV/HCV trial. Patient demographics, characteristics, SVR12 and discontinuation data has been compared.

Results: The ION-3 post-hoc analysis reported 123 patients who were TN, NC and VL<6M and treated with 8 weeks of LDV/SOF. Mean age was 52, 22% black, 72% GT1a; the SVR12 was 97% (119/123). The overall SVR12 rate from six diverse real world and post marketing cohorts was also 97% (638/658). There was no significant impact of HCV genotypes or subtypes (GT1a, 1b versus GT4), prior treatment history, presence or absence of cirrhosis, high viral load (HCV VL>6M), or HIV/HCV co-infection. All response rates are detailed in Figure1.

Conclusions: LDV/SOF for 8 weeks yielded high SVR rates in ION-3. Analysis of RWE data from several diverse and heterogeneous cohorts from the US & EU show SVR outcomes that were consistent with the ION-3 results and supports the use of 8 weeks LDV/SOF in treatment-naive, non-cirrhotic GT1 patients with a baseline HCV VL <6M and possibly in other populations including HIV/HCV co-infected patients. Discontinuation rates were low despite diverse patients and clinical settings. Data from the TARGET and TRIO cohorts also suggests that the 8-week regimen is underutilized.

Keywords: Phase 3, Real World Effectiveness, Ledipasvir, 8 weeks

PE - 040

False Positive Rates of Conventional Screening Test for Hepatitis C Virus Infection in Low Prevalent Area

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Aims: Hepatitis C virus (HCV) infection is screened by immunoassays. However, false positive results of anti-HCV occur with unacceptable frequency, especially in low-prevalence populations. This study was aimed to evaluate the efficacy of screening test for HCV infection and determine anti-HCV signal-to-cutoff (S/CO) ratios to discriminate true-positive from false-positive anti-HCV infection.

Methods: A total of 77,571 patients who were tested anti-HCV from 2010 to 2015 were evaluated. False-positive (FP) anti-HCV was defined as samples with negative or indeterminate RIBA results and HCV RNA negativity. True-positive (TP) anti-HCV was defined as positive RIBA or positive HCV RNA. Receiver-operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of anti-HCV S/CO ratio for predicting HCV viremia, and for discriminating true-positive from false-positive anti-HCV infection.

Results: Anti-HCV positive rate was 1.45% (1126/77571). Among the 632 patients who were tested HCV RNA and/or RIBA, 32.1% (203/632) of the patients showed false-positive antibody results. There were significant differences in serum ALT level, anti-HCV S/CO ratio and RIBA results (viremia vs. non-viremia, TP vs. FP). Using ROC curves, the optimal cutoff values of anti-HCV S/CO ratio for HCV viremia and TP were 8 and 6, respectively. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for diagnosing HCV viremia at 8.0 of anti-HCV S/CO ratio were 98.0%, 88.4%, 91.6% and 97.2%, respectively. Those for TP at 6 of anti-HCV S/CO ratio were 90.7%, 99.0%, 99.5% and 83.4%, respectively. Using the level of 6 of anti-HCV S/CO ratio, anti-HCV positive rate was changed to 0.75%.

Conclusions: False positive rate was very high. Therefore, diagnostic strategy of HCV infection should be changed according to anti-HCV S/CO ratio in Korean population.

Keywords: Hepatitis C, PCR, Immunoblot, Prevalence

PE - 041

Long-term Follow-up of Patients with Chronic HCV Following Treatment with DAAs: Maintenance of SVR, Persistence of Resistance and Clinical Outcomes

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Aims: Significant advances in the treatment of chronic hepatitis C have been made with direct acting antiviral (DAA) regimens. While SVR rates may now be achieved in the majority of patients, data describing long-term virologic and clinical outcomes with these regimens are needed.

Methods: We report interim data from two 3-year registry studies capturing long-term outcomes in patients with chronic hepatitis C treated with DAAs. Subjects are enrolled into two registries according to SVR status; SVR (SVR registry) versus non-SVR (Sequence registry). We determined the durability of SVR, relapse and reinfection rates. The persistence of resistance associated variants (RAVs) in treatment failures is followed. Liver disease progression is assessed by periodic clinical & labroratory evaluations.

Results: 5433 patients enrolled in the SVR registry with a median

	SVR Registry N=5433	Sequence Registry (non-SVR) N=536
Age, years (SD)	54 (9.9)	54 (8.0)
Male, n (%)	3405 (62.7)	417 (77.8)
Cirrhosis, n (%)	1088 (20.0)	117 (21.8)
Race, n (%)		
Caucasian	4621 (85.1)	448 (83.6)
African Descent	516 (9.5)	66 (12.3)
IL28B Genotype, n (%)		
CC	1608 (29.6)	119 (22.2)
CT	2826 (52.0)	290 (54.1)
TT	841 (15.5)	106 (19.8)
HCV Genotype, n (%)		
1	3618 (66.6)	333 (62.1)
2	535 (9.8)	27 (5.0)
3	1014 (18.6)	170 (31.7)
4	143 (2.6)	5 (1.0)
5	31 (<1)	1 (<1)
6	27 (<1)	0

(range) follow-up of 71 (0-156) weeks. 536 patients enrolled in the Sequence registry with a median (range) of follow-up of 44 (0-159) weeks. Demographic and disease characteristics are described below. In the SVR registry, at the time of data analysis, 99.7% (5414/5433) of patients have maintained SVR with 0.3% (19/5433) having emergent virus (6 relapses, 8 new infections, 5 to be confirmed). Viral emergence occurred by Week 96 in all patients. In the Sequence registry of 89 patients who received an NS5A inhibitor and had baseline sequencing data, 91.0% (81/89) had NS5A RAVs at Week 96. HCC was reported in 0.3% (16/5433) and 0.9% (5/536) of patients in the SVR and Sequence registries through Week 96 respectively. There were no significant changes in laboratory evaluations or liver disease assessments.

Conclusions: SVR achieved following treatment with DAA regimens is durable. In patients failing NS5A-containing regimens, treatment-emergent NS5A RAVs persist. Rates of clinical disease progression and HCC are low. Ongoing reporting from these registry studies will be required to confirm these findings.

Keywords: Long-term outcomes, DAA, SVR, Resistance

PE - 042

Epidemiology and Genotype Distribution of HCV in Mongolia

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Aims: Mongolia is a unique country with high endemicity for three blood borne hepatitis viruses, namely HBV, HCV and HDV. The number of patients with acute hepatitis decreased considerably with an estimated annual number of cases 13,000/ year in 1991 to 1700/year in 2013 in Mongolia.Hepatitis B and C virus infection are one of the major causes of liver cirrhosis and HCC in Mongolia. However, viral hepatitis C is still one of the serious public health concerns in Mongolia.

To investigate of HCV infection among apparently healthy populations in Mongolia.

Methods: The study population was consisted of 1512 subjects from 13 provinces and Ulaanbaatar city which is the capital city of Mongolia, and the age ranged from 0 to 80 years.

Results: According to our study results, the prevalence of anti-HCV was 15.6%, and the HCV RNA was detected in 11 %; therefore, we can say that the prevalence of this infection is very high in Mongolia.The prevalence of anti-HCV and HCV RNA had a tendency to increase with age. The prevalence of anti-HCV and HCV RNA in population aged over 61 years was significantly higher than those aged 31 to 40 year. The history of dental care, surgery, and tattooing was significantly more frequent in anti-HCV positive subjects compared with anti-HCV negative subjects. Interestingly, the most of HCV infection is caused by genotype 1. However, Genotype 2 of HCV is very rare, less than 2 percent in Mongolia. The extreme predominance of HCV genotype 1b in the Mongolian population may be explained by the greater ethnic and genetic homogeneity of current Mongolian population.

Conclusions: The epidemiological situation of HCV infection in Mongolia is catastrophic. This infection was evenly distributed in all areas and has endemic characteristics for the country. The rate of positive anti-HCV and HCV-RNA was increasing age-dependently. The predominant genotype of HCV in Mongolia is 1b.

Keywords: HCV, Genotype, Mongolia

PE - 043

Treatment Outcomes on Chronic Hepatitis C Virus in Mongolia

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Aims: Chronic HCV infection is a major cause of cirrhosis, hepatocellular carcinoma HCC), and liver transplantation in Mongolia. HCV disease progression modeling was used to quantify the future disease burden.

Methods: HCV infection and related sequelae were tracked between 1950 and 2030. Baseline assumptions were extracted from the literature, using Mongolian data where available. Scenarios were developed to reduce future burden of HCV infection by increasing treatment eligibility and sustained virological response (SVR) rates, and increasing the annual treated population.

Results: In 2013, there were an estimated 200,000 viremic HCV infections, which is expected to decline by 17% (165,000) by 2030 due to mortality as the infected population ages and progressed to more advance stages of liver disease. In the same period, the prevalence of advanced liver disease is expected to increase by 30% while liver related deaths will increase by 25%.

A scenario was modeled where SVR rates increase to 95% in 2016, with treatment restricted to individuals aged 40-59 years with fibrosis stage ≥F2. The overall impact on mortality and morbidity was less than 1% due to very low treatment rate (200 cases annually).
A second scenario included increased SVR, along with increases in the annual treated population up to 25,000 treated in 2022. Over time, treatment was extended to individuals aged 15-74 years, and included all fibrosis stages. Chronic infections were reduced to 20,000 by 2025 (90% reduction). Liver-related mortality decreased by 85% (11,000 deaths averted) while cases of decompensated cirrhosis and HCC decreased 75-85% by 2025 and 85-90% by 2030.
Conclusions: HCV prevalence in Mongolia will decrease by 2030, but cases of advanced liver disease will continue to rise. Increasing treatment with high SVR therapies can lead to significant reduction in total infections, mortality, and morbidity.
Keywords: Mongolia, HCV, Genotype, Treatment

PE - 044

The Efficacy and Safety of Daclatasvir and Asunaprevir for Hepatitis C Virus Genotype 1 Infection in Old Age Patients with Compensated Cirrhosis

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Aims: Treatment strategy of hepatitis C virus (HCV) has been changed rapidly ever since the introduction of direct acting antivirals such as daclatasvir (DCV) and asunaprevir (ASV). In this study, we evaluated the efficacy and safety of DCV/ASV for HCV in real-life practice.
Methods: Patients were treated by 60 mg of DCV once daily plus 200mg of ASV twice daily for 24 weeks and followed for 12 weeks. The primary endpoint was sustained virological response at 12 weeks after treatment (SVR12) and safety.
Results: This retrospective study included 8 patients with chronic HCV genotype 1b infection. All enrolled patients were diagnosed as liver cirrhosis and their mean age was relatively old (65.75 years). One patient was nonresponder and two patients relapsed with previous PegIFN/RBV treatment. 88% of SVR12 was achieved by the DCV/ASV combination therapy. Serum transaminase levels and aspartate aminotransferase to platelet ratio index (APRI) were improved after the treatment administration. DCV and ASV were well tolerated among the majority of patients and discontinuation of the treatment due to adverse events (elevated liver enzyme, decompensation) was occurred in two patients.
Conclusions: In this study, DCV/ASV treatment achieved high sustained virological response with few adverse events even in those with cirrhosis, advanced age, and nonresponsive/relapsing to previous interferon based therapy. Close monitoring of safety may be necessary when treating chronic hepatitis C patients receiving DCV and ASV, especially with old age and cirrhosis
Keywords: Hepatitis C virus, Liver cirrhosis, Daclatasvir, Asunaprevir

PE - 045

Clinical Adherence to KASL Guidelines for the Management of Adverse Events in Treating Chronic Hepatitis C with Interferon Based Regimen

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Aims: Although direct acting antivirals have been emerged in Korea, peginterferon and ribavirin is still remained as a therapeutic option for treating chronic hepatitis C. We surveyed to evaluate the adherence to KASL guideline for the management of adverse events in treating chronic hepatitis C with interferon based regimen.
Methods: A nationwide survey study to hepatologists and gastroenterologists at general hospital or tertiary university hospital was conducted from June, 2014 to August, 2014. A survey was performed with questionnaire composed of 25 items regarding clinical practice and therapeutic options for adverse events of peginterferon and ribavirin.
Results: Among 120 physicians surveyed, 71 eligible questionnaires returned and completed surveys. Most of the physicians (87.3%) were occupied at tertiary university hospital and mean clinical practice term was 12.1 years (1-41 years). Most physicians agreed to stop or reduce peginterferon according to KASL guidelines regarding neutropenia and thrombocytopenia (70.5%, 81.7%, respectively). However, lesser physicians of 58% agreed to stop or reduce ribavirin according to KASL guideline regarding anemia. Some physicians have answered that they choose erythropoietin or transfusion instead of handling ribavirin in the anemic condition (n=3, 4.2%). Physicians with longer clinical practice term tend to be lesser adherent to KASL guideline regarding anemia in terms of handling ribavirin. Before starting peginterferon and ribavirin, 95.8% physicians evaluated TSH and free T4 level for evaluating thyroid disease, and 77.5% monitored TSH and free T4 regularly with 2-4 month intervals as suggested in KASL guideline. Pretreatment evaluation of psychiatric problems such as depression was done in 72% physicians. However, lesser physicians performed evaluating cardiac and pulmonary diseases before starting treatment (64.8%, 66.2%, respectively).
Conclusions: This is the first national survey to examine the adherence to KASL guideline for the management of adverse events in treating chronic hepatitis C with interferon based regimen.
Keywords: Chronic hepatitis C, Peginterferon, Ribavirin, Adverse events

PE - 046

Nationwide Seroepidemiology of Hepatitis C Virus Infection in South Korea, Data from National Health and Nutrition Examination Survey 2012~2014

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Aims: The prevalence of hepatitis C in South Korea was reported to be 0.78~1.7%. However, most studies were based on the data from heath check examinees. We investigated the prevalence of hepatitis C virus (HCV) infection in general population.

Methods: We analyzed the weighted prevalence of anti-HCV antibodies in Korean aged ≥ 10 years on the data from the Korea Health and Nutrition Examination Surveys between 2012 and 2014 by ages, gender, and area. The proportion and features of subjects with HCV viremia was also investigated

Results: A total of 140 persons had positive anti-HCV among 17,764 examinees. The overall weighted prevalence of HCV Ab was 0.62% (95% confidence interval (CI) 0.49~0.78, n=255,987/41,139,005) in persons aged ≥ 10 years and 0.68 % (95% CI 0.54~ 0.86, n=245,317/36,022,181) in persons aged ≥ 20 years. Anti-HCV prevalence in women (0.72%) was higher than that in men (0.52%). Gradual increase in anti-HCV positivity was observed, from 0.13% in those aged 20-29 years to 1.87% in those ≥ 70 years. The weighted prevalence of anti-HCV varied among different areas, being higher in Busan (1.14%), Choongbuk (1.25%), Ulsan (1.48%) and Gyeongnam (1.82%), and lower in Jeju (0%). Among anti-HCV positive subjects, serum HCV RNA was detected only in 32.5%. Subject with positive anti-HCV and detectable HCV RNA had higher value of serum aminotransferase and signal/cutoff ratio of anti-HCV than those with positive anti-HCV and undetectable HCV RNA.

Conclusions: The prevalence of HCV infection in Korean general population was lower but had comparable gender and age distrubution compared with previous reports mostly based on data from health check examinees.

Keywords: Hepatitis C, Prevalence, Korea, General Population

PE - 047

Efficacy and Safety of Ombitasvir, Paritaprevir/Ritonavir, and Dasabuvir without Ribavirin in Patients with HCV Genotype 1b: Pooled Analysis

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Aims: Ombitasvir (OBV), paritaprevir with the pharmacokinetic enhancer ritonavir (PTV/r), and dasabuvir (DSV) without ribavirin (RBV) has demonstrated sustained virologic response at 12 weeks post-treatment (SVR12) rates of 99-100% in HCV GT1b-infected patients without cirrhosis. In GT1b-infected patients with cirrhosis, OBV/PTV/r + DSV with RBV for 12 weeks achieved an SVR12 rate of 98.5%. Regimens with RBV are associated with higher rates of adverse events (AEs), primarily anaemia, and a higher pill burden. This post hoc, pooled analysis from 5 Phase 3/3b trials investigated the efficacy and safety of the RBV-free, 12-week regimen of OBV/PTV/r + DSV among HCV GT1b-infected patients with or without compensated cirrhosis.

Methods: Data for patients treated without RBV in 5 trials (GT1b-infected patients with cirrhosis: TURQUOISE-III; GT1b-infected patients without cirrhosis: PEARL-II, PEARL-III, TOPAZ-II, MALACHITE-I) were pooled and patients were characterised by the presence or absence of compensated cirrhosis at baseline. Treatment-naive and pegylated interferon/RBV-experienced patients were included in the analysis population. Efficacy and safety were assessed in all patients. Comparisons of safety outcomes between groups were analysed using Fisher's exact test.

Results: The pooled analysis included 60 patients with cirrhosis and 521 patients without cirrhosis: 62% and 48% were male, 87% and 91% were white, and 45% and 74% were treatment-naive, respectively. SVR12 with OBV/PTV/r + DSV for 12 weeks was 100% (60/60) and 99% (515/521) in patients with and without cirrhosis, respectively. Three patients without cirrhosis experienced virologic failure. Treatment-emergent AEs and laboratory abnormalities are provided in the following table.

Table 1. Treatment-emergent AEs and laboratory abnormalities

	With cirrhosis n=60	Without cirrhosis n=521	P-value
Serious AE*, n (%)	1 (2)	8 (2)	
AE leading to study drug discontinuation, n (%)	0	0	NS
AEs in ≥10% of either patient group, n (%)			
Headache	11 (18)	107 (21)	NS
Fatigue	13 (22)	98 (19)	NS
Diarrhoea	12 (20)	38 (7)	0.003
Pruritus	6 (10)	42 (8)	NS
Insomnia	6 (10)	18 (4)	0.029
Dizziness	6 (10)	15 (3)	0.015
Arthralgia	6 (10)	12 (2)	0.007
Post-baseline laboratory abnormalities, n (%)			
Haemoglobin			
Grade 2 (<10.0-8.0 g/dL)	1 (2)	0	NS
Grade 3 (<8.0-6.5 g/dL)	0	0	NS
Grade 4 (<6.5 g/dL)	0	0	NS
ALT			
Grade 3 (>5–20 x ULN)	1 (2)†	1 (0.2)†	NS
Grade 4 (>20 x ULN)	0	0	NS
Total bilirubin			
Grade 3 (>3–10 x ULN)	0	1 (0.2)	NS
Grade 4 (>10 x ULN)	0	0	NS

AE, adverse event; Grade, CTCAE; NS, not significant; ULN, upper limit of normal.
** Serious AEs: arthritis; hypotension (both related to study drug with reasonable possibility); cellulitis; nephrolithiasis; endometrial polyp; myalgia; ductal carcinoma in situ; pericarditis; fractured ribs*
† Two patients experienced grade 3 ALT elevations; both events were transient, did not result in discontinuation of treatment, and both patients achieved SVR12.

Conclusions: In HCV GT1b-infected patients, SVR12 rates with the RBV-free, 12-week regimen of OBV/PTV/r + DSV were very high in patients with and without compensated cirrhosis (100% and 99%). Treatment was well tolerated, with no discontinuations due to an AE, and there were low rates of serious AEs and grade 3/4 laboratory abnormalities.

Keywords: HCV GT1b, Ombitasvir, Paritaprevir/ritonavir, Dasabuvir

PE - 048

ONYX-II: Efficacy of Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir + Ribavirin in HCV Genotype 1b-Infected Patients with Compensated Cirrhosis from South Korea and Taiwan

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Background: Chronic hepatitis C virus (HCV) infection is associated with development of complications including hepatocellular carcinoma, liver failure and cirrhosis. Patients with cirrhosis are historically more difficult to cure. In southeastern Asia, the most prevalent HCV genotype (GT) is GT1b. In western populations, the 3 direct-acting antiviral (3-DAA) regimen of ombitasvir (OBV), ritonavir-boosted paritaprevir (PTV/r; identified by AbbVie and Enanta) and dasabuvir (DSV) ± ribavirin (RBV) demonstrated sustained virologic response (SVR) at post-treatment week 12 (SVR12) rates of 99% in patients with GT1b infection and compensated cirrhosis regardless of prior treatment experience. The regimen, however, has not been investigated in southeastern Asian populations. The ONYX-II study is evaluating the efficacy and safety of this regimen in Asian patients with HCV GT1b infection and compensated cirrhosis.

Methods: Treatment-naïve and interferon-based therapy-experienced patients with HCV GT1b-infection and compensated cirrhosis were enrolled in South Korea, Taiwan, and China, and received 12 weeks of OBV/PTV/r (25 mg/150 mg/100 mg once daily) and DSV (250 mg twice daily) with RBV (weight-based). Patients will be followed for 48 weeks after the last dose of study drugs. The primary objectives are to compare the SVR12 rate to the known SVR rate of telaprevir + peg-interferon (IFN) + RBV therapy, and to assess the safety of OBV/PTV/r + DSV + RBV.

Results: Twenty-one and 20 subjects were enrolled in South Korea and Taiwan, respectively. Of South Korean patients, 52% were male and 71% were treatment-experienced; of Taiwanese patients, 45% were male and 65% were treatment-experienced. Safety data and SVR at post-treatment week 4 (SVR4) will be available for presentation.

Conclusions: The ONYX-II study evaluates the 3-DAA regimen of OBV/PTV/r + DSV with RBV for Asian patients with compensated cirrhosis and HCV GT1b infection. Resultant data may provide evidence for treatment guidelines for HCV GT1b in this population.

Keywords: Hepatitis C, Efficacy, Direct-acting antiviral, SVR

PE - 049

Analysis of Hepatitis C Virus NS3 and NS5A Resistance Mutations after Daclatasvir plus Asunaprevir Treatment Failures in Korea

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Aims: Daclatasvir plus asunaprevir treatment is the first direct-acting antiviral (DAA) treatment in Korea for the genotype 1b chronic hepatitis C patients. Despite its high sustained virologic response (SVR), emergence of resistance mutations is still a serious problem. In this study, resistance mutations of hepatitis C virus NS3 protease and NS5A were analyzed for the patients who had failed in daclatasvir plus asunaprevir treatment in Korea.

Methods: Blood samples were collected from the 5 patients who had failed in daclatasvir plus asunaprevir treatment. Viral RNA was isolated from the blood samples and NS3 protease domain and NS5A domain I were amplified by RT-PCR. The amplified DNA fragments were read by direct sequencing reactions and the resistance mutations were identified by comparing to the genotype 1b Con1 isolate sequence.

Results: A well-known Y93H mutation of NS5A was observed in 4 out of the 5 treatment failures. Substitution mutations at Leu 31 (Val or Met) of NS5A were also observed in 3 out of the 4 Y93H-containing blood samples. However, one sample did not have any substitution mutations at Leu 31 and Tyr 93. Instead, it had a deletion mutation at Pro 32. Sequencing of NS3 protease domain found substitution mutations at Asp 168 (Tyr, Glu, Ala, or Val) in the 5 treatment failures. Apart from these well-known resistance mutations of NS3 and NS5A, other mutations were also found compared to the genotype 1b Con1 isolate sequence.

Conclusions: Resistance mutations against the daclatasvir plus asunaprevir treatment were identified among Korean patients by this study. The data collected from this investigation would help select retreatment options and could identify additional mutations that had not been identified in the previous clinical trials.

Keywords: Hepatitis C virus, Daclatasvir, Asunaprevir, Resistance mutation

PE - 050

Resistance Analyses for Ledipasvir/Sofosbuvir Containing Regimens in HCV-infected Patients Who Have Advanced Liver Disease or Are Post Liver Transplant

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SVR 12 (%)	Post-transplantation with F0-F3 fibrosis or compensated cirrhosis		Pre or post-transplantation with decompensated cirrhosis (CPT B or C)		Overall
	12 weeks	24 weeks	12 weeks	24 weeks	
	GT 1 HCV-infected patients				
Patients with NS5A RAVs	23/23 (100%)	21/21 (100%)	19/24 (79%)	33/33 (100%)	96/101 (95%)
Patients with no NS5A RAVs	133/136 (98%)	132/132 (100%)	106/112 (94.6%)	100/106 (94%)	471/486 (97%)
	GT 4 HCV-infected patients				
Patients with NS5A RAVs	9/9 (100%)	6/6 (100%)	2/5 (40%)	5/5 (100%)	22/25 (88%)
Patients with no NS5A RAVs	1/1 (100%)	4/4 (100%)	4/4 (100%)	1/1 (100%)	10/10 (100%)

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Aims: Ledipasvir/sofosbuvir (LDV/SOF) with ribavirin (RBV) demonstrated high SVR rates in patients with chronic hepatitis C (HCV) genotype (GT) 1 or 4 infection who have decompensated cirrhosis or who have undergone liver transplantation. Here we evaluated the effect of baseline HCV NS5A and NS5B resistance-associated variants (RAVs) on treatment outcome and characterized the viral resistance in all virologic failures.

Methods: Deep sequencing with a 1% assay cut-off was performed for NS5A and NS5B at baseline for all the patients and at the time of virologic failure for those who relapsed.

Results: Out of 625, 622, and 619 samples were analyzed for baseline NS5A and NS5B respectively. Table 1 summarizes SVR12 rates by treatment duration and the presence or absence of baseline NS5A RAVs. NS5B RAVs at baseline were uncommon, occurring in 4.8% (28/586) GT1 patients and 3.2% (1/31) GT 4 patients. Of these 29 patients, only one GT1 patient with CPT C cirrhosis who had L159F at baseline and was treated for 24 weeks with LDV/SOF+RBV did not achieve SVR12. NS5A RAVs at positions 24, 28, 30, 31, 58, and 93 were enriched or emerged in 20/22 (91%) GT1 and 1/3 GT4 infected patients with virologic failure. The NS5B NI RAV E237G emerged in 3 GT1a patients and 1 GT4d patient at the time of relapse (4/23, 17%).

Conclusions: The presence of baseline NS5A or NS5B RAVs did not impact the treatment outcome to 12 or 24 weeks of LDV/SOF+RBV in GT1 or GT4 HCV patients with liver ransplantation without decompensated liver disease, or 24 weeks of LDV/SOF+RBV in patients with decompensated cirrhosis. Lower SVR rates were observed among the limited number of patients with decompensated cirrhosis and baseline NS5A RAVs who received 12 weeks of LDV/SOF+RBV treatment.

Keywords: Ledipasvir/Sofosbuvir, Decompensation, Post LT, Resistance

PE - 051

Daclatasvir and Asunaprevir Combination Therapy for Chronic Hepatitis C Virus Genotype 1b Infection in Real World

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Aims: Recently, treatment of hepatitis C virus (HCV) has evolved and improved remarkably. Use of all-oral combination regimens of direct-acting antivirals (DAAs) in chronic hepatitis C (CHC) patients shows a sustained virologic response (SVR) rate of ≥90%. Daclatasvir (DCV) plus asunaprevir (ASV) combination therapy has produced high rates of SVR among HCV genotype 1b patients without baseline NS5A resistance-associated variants (RAVs) in clinical trials.

We evaluated the efficacy and safety of DCV and ASV combination therapy for chronic HCV genotype 1b infection in real world.

Methods: We retrospectively reviewed the medical records of patients with chronic HCV genotype 1b infection**.** A total of 86 patients (57 treatment-naïve patients), who were treated with DCV and ASV combination at their recommended doses, were enrolled in this study. We evaluated the virologic response rates at week 4, 12, 24 of treatment, and week 12 after completion of treatment (SVR12).

Results: The mean age was 58.52±9.78 years, and 41 patients (47.7%) were men. Thirty patients (34.9%) had cirrhosis. Baseline NS5A sequences were available from 80 patients. Pretreatment NS5A RAVs were present in 4 patients (5.0%). DCV plus ASV provided virologic response in 73 patients (100%) at week 4; 55 patients (96.5%) at week 12; 18 patients (94.7%) at week 24 of treatment; one patient (100%) at week 12 after completion of treatment. Adverse events occurred in 6 patients. Adverse events included headache, nausea, diarrhea, and skin rash. No serious adverse events occurred.

Conclusions: DCV and ASV combination therapy provided high rates of virologic response at week 4, 12, 24 of treatment, and week 12 after completion of treatment in chronic HCV genotype 1b infection patients in real world. DCV plus ASV was well tolerated without serious adverse events. We also expect high SVR rate after DCV plus ASV treatment in a large number of cases.

Keywords: Chronic hepatitis C, Daclatasvir, Asunaprevir

PE - 052

Implications of OraQuick Anti-HCV Test for Rapid Detection of Hepatitis C in Outpatient Gastroenterology Clinics

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Aims: Recently, simple, point-of-care, rapid diagnostic test was introduced instead of laboratory-based enzyme immunoassay to facilitate anti-HCV antibody screening. We aimed to access the acceptability and feasibility of rapid HCV test and to determine the awareness of hepatitis C in patients with abnormal liver function.

Methods: The OraQuick anti-HCV test (OraSure Technologies Inc., Bethlehem, PA, USA) was evaluated in prospective testing of patients with abnormal liver function using oral fluid at four medical centers in Korea. All patients completed the questionnaire on satisfaction with using rapid HCV tests and awareness of hepatitis C.

Results: At the time of the abstract, 308 patients were enrolled. The median age was 52.0 years (range 18 - 79 years and 174 were males. Seven patients (2.8%) were reactive according to the oral fluid OraQuick anti-HCV test. HCV RNA PCR was detected in 6 of them. Two patients had invalid tests the first time, but the

second time, one was OraQuick positive (HCV RNA PCR positive) and the other was negative. Most patients agreed that they were satisfied with a rapid diagnostic test (89.6%) and that they would recommend this to an acquaintance (91.9%). Only 37.7% were aware of hepatitis C.

Conclusions: The OraQuick anti-HCV test using oral fluid could be beneficial as a screening tool.

Keywords: HCV, Rapid test, Oral fluid, Awareness

PE - 053

Time-degenerative Factors and the Risk of Hepatocellular Carcinoma after Antiviral Therapy among HCV Patients: A Model for Prioritization of Treatment

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Aims: Age and hepatic fibrosis are the factors that increase the risk of hepatocellular carcinoma (HCC) over time. We aimed to explore their impac at the initiation of antiviral therapy on HCC among chronic hepatitis C (CHC) patients.

Methods: A total of 1281 biopsy-proven CHC patients receiving interferon-based therapy were followed for a mean period of 5.5 years.

Results: The 5-year cumulative incidence of HCC did not differ between non-SVR and SVR patients who were <40 years old (7.7 % vs. 0.5%, P=0.1), but was significantly higher in non-SVR patients between 40 and 55 years old (18.0% vs. 1.3%, P<0.001) and >55 years old (15.1% vs. 7.9%, P=0.03). Compared with SVR, non-SVR was independently predictive of HCC in patients 40-55 years old (hazard ratio [HR]/95% confidence intervals [CI]: 10.92/3.78-31.56, P<0.001) and >55 years old (HR/CI: 1.96/1.06-3.63, P=0.03) but not in patients <40 years old (HR/CI: 2.76/0.41-18.84, P=0.3). The 5-year cumulative incidence of HCC did not differ between non-SVR and SVR patients whose fibrosis stage was F0-1 (4.6% vs. 1.9%, P=0.25) but was higher in non-SVR patients with F2-3 (21.4% vs. 4.3%, P<0.001) or F4 (33.5% vs. 8.4%, P=0.002). Compared with SVR, non-SVR was independently predictive of HCC in patients with F2-3 (HR/CI: 4.36 /2.10-9.03, P<0.001) and F4 (HR/CI: 3.84/1.59-9.30, P=0.03) but not in those with F0-1 (HR/CI: 1.53/ 0.49-4.74, P=0.47).

Conclusions: Delayed HCV clearance for patients with CHC > 40 years old or with a fibrosis stage > 2 increases the risk of HCC over time.

Keywords: HCC, HCV

Liver Cancer, Basic

PE - 054

Association of Microrna Machinery Genes with Hepatocellular Carcinoma in a Korean Population

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Aims: Single-nucleotide polymorphisms (SNPs) in microRNA machinery genes might affect microRNA processing and subsequently impact tumorigenesis. The aim of this study was to investigate the associations between SNPs in microRNA machinery genes and hepatocellular carcinoma (HCC) in a Korean population.

Methods: Genotyping of six SNPs in microRNA machinery genes was performed using blood samples from 147 patients with HCC and 209 healthy control subjects.

Results: None of the six SNPs in microRNA machinery genes were significantly associated with HCC development. However, among the models for six polymorphic loci-DICER (rs3742330 and rs13078), DROSHA (rs10719 and rs6877842), RAN (rs14035) and XPO5 (rs11077)-one allele combination (A-A-T-C-C-C) showed synergistic effects in terms of an increased risk of HCC development (odds ratio=8.881, 95% confidence interval [CI]=1.889-41.750; P=0.002). Multivariate Cox proportional hazard regression analysis showed a significant survival benefit for the DICER rs3742330 GG compared with the AA genotype (hazard ratio [HR], 0.352; 95% CI, 0.155-0.796; P=0.013) and for the RAN rs14035 CT compared with the CC genotype (HR, 0.599; 95% CI, 0.363-0.988; P=0.046).

Conclusions: Although we found no direct association between DICER (rs3742330 and rs13078), DROSHA (rs10719 and rs6877842), RAN (rs14035) or XPO5 (rs11077) polymorphisms and HCC risk, we demonstrated that DICER (rs3742330) and RAN (rs14035) were associated with the survival of HCC patients. Future studies with larger samples are needed to determine the associations of SNPs in microRNA machinery genes with HCC risk and prognosis.

Keywords: Hepatocellular carcinoma, MicroRNA machinery gene, Single nucleotide polymorphism

PE - 055

Differential Tumorigenic Effects by C-Myc Mutants in Liver Cancer

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Aims: Liver cancer is a major health concern worldwide, ranking third in terms of cancer-related mortality. The c-Myc gene is epigenetically altered in almost 50% of human liver cancers, leading to persistent over-expression of cMyc. In addition to quantitative changes of cMyc protein in cancers, mutation leading to amino acid substitution of cMyc has been found in a certain type of cancers. In this study, we compared tumorigenic potentials among c-Myc mutants in the liver.

Methods: Transgenic liver cancer mouse models expressing different c-Myc mutants were developed using hydrodynamic transfection. Transposon vectors encoding the wild-type c-Myc, c-MycT58A, and c-MycS71F were constructed. To induce liver cancer, 20 μg of transposons were mixed with plasmids expressing the Sleeping Beauty transposase and then diluted in 2.5 ml of 0.9% saline. The DNA mixtures were injected into the lateral tail veins of 6-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.
Results: Hepatocellular carcinomas (HCC) were induced by the stable expression of c-Myc and shp53. Wild type c-Myc was less tumorigenic than c-Myc2T58A or c-Myc2S71F when co-expressed with shp53. The c-Myc mutant groups, c-Myc2T58A or c-Myc2S71F died earlier than the c-Myc wild type group ($p< 0.05$). There was no difference in phenotypes of malignant hepatocytes among tumors induced by cMyc mutants and wild-type.
Conclusions: Co-expression of c-Myc and shp53 in the mouse liver promoted hepatocarcinogenesis. Wild type c-Myc was less tumorigenic than c-Myc2T58A or c-Myc2S71F under the condition that P53 was down-regulated.
Keywords: HCC, C-Myc, Hydrodynamic Injection, Sleeping beauty transposon

PE - 056

Changes in Immunologic Function after Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

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Aims: Transarterial chemoembolization (TACE) is widely used as a treatment modality for intermediate stage of hepatocellular carcinoma (HCC). Although several studies showed enhanced natural killer (NK) cell response after local treatment for HCC have been reported, knowledge of impact on NK cell after TACE is still unrevealed. The aim of this research was to investigate immunologic changes after TACE in HCC patients.
Methods: Total 23 patients undergoing TACE for hepatocellular carcinoma were enrolled. Absolute counts of peripheral blood lymphocytes followed by phenotypic and functional characterization of NK cell population were carried out the day before, 1 and 4 weeks after TACE.
Results: Peripheral blood lymphocytes kinetics revealed decrease of NK cell population at 1 week after TACE from the baseline (4.18% at 1 week vs. 9.54% at baseline, P=0.047), and restoration of NK cell population at 4 week after TACE from 1 week after TACE (12.24% at 4 week vs. 4.18% at baseline, P=0.040). This was along with significantly increased level of inhibitory NK receptor, NKG2A, at both time points of 1 week and 4 week after TACE from the baseline (20.24% at 1 week from 4.26% at baseline, P<0.001; 23.92% at 4 week from 4.26% at baseline, P<0.001), while there were no significant changes in activating NK receptors. Anti-K562 cell cytotoxicity appeared consistently decreased in terms of absolute activity at 1 week after TACE as compared to baseline, and showed a tendency to restore at 4 weeks after TACE.
Conclusions: Unlike previously reported immunologic changes in patients with local treatment for HCC, immunologic function seems to be compromised shortly after TACE. This result suggests that various therapeutic strategies can have different effects on body immune function, and better understanding of the changes in the immune system in HCC patients will promise better tumor control.
Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Natural killer cell, Immunologic change

PE - 057

First Experience of Using Two-stage Resection of the Liver (Split in situ) in Patients with Metastatic Colorectal Cancer

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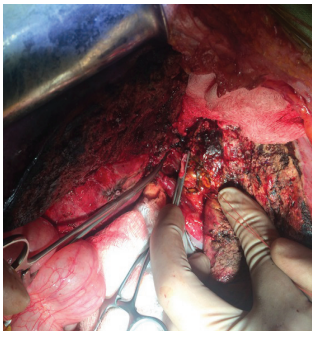
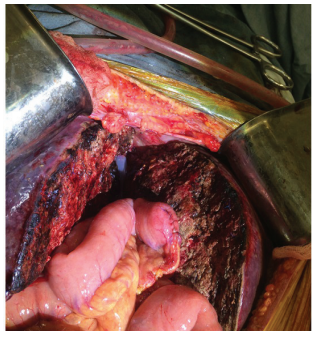
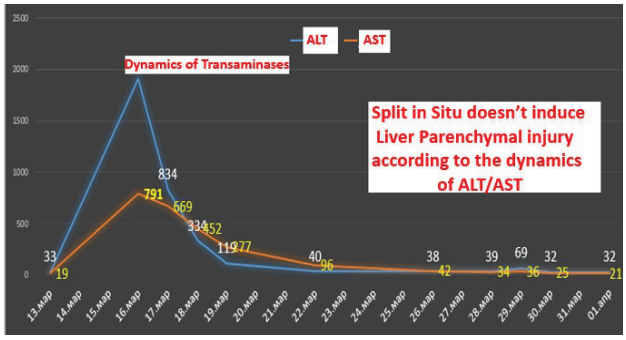
National Oncology & Transplant Center

Aims: To present the first in Kazakhstan performed split in situ surgical procedure in a patient with sT4aN2bMOG2 colorectal cancer at National Oncology & Transplant Center.
Introduction: Two-stage liver surgery with preliminary right portal vein occlusion procedure (ligation or embolisation) became standard in clinical practice and allows liver resections in 60-82% of initially inoperable patients. Right portal vein ligation with concomitant liver partition in situ (in situ splitting, ISS) is innovatory and promising approach. This case report of a 67 y.o. male with three colon meta-







stasis in right liver lobe.
Methods: A case report of the patient's two-stage surgical procedure and results
Results: Right portal vein ligation and in situ splitting was performed in 67 years old male with three colon metastases in right liver lobe (figure-1) and insufficient volume of future liver remnant (FLR/SLV = 550/1294=29%). After completion of dissection of liver parenchyma and portal vein ligation subsequent hepatico-jejunoanostomosis was performed as shown in figure-2. The early post-first operative period went without complications. CT angiography on 11th postoperative day showed left liver lobe hypertrophy rate of 58% (FLR/SLV = 750/1294) and left liver lobe volume increase from 29 to 58%. During surgery the left liver hypertrophy was seen (as shown in figure-3), there was no visible parenchymal injury in observation during laparotomy. Right hemihepatectomy was performed on day 13 after the first stage. There were no signs of postoperative liver failure. According to the dynamical transaminases (shown in the figure-2) in situ split procedure doesn't induce liver injury.
Conclusions: New two-stage surgery approach (ISS) can decrease number of patients who were
inoperable because of insufficient volume of future liver remnant and high risk of postoperative liver failure.
Keywords: Liver cancer, Split in situ, Remnant, Liver surgery

PE - 058

Roles of SS18L1 Polymorphisms in Predicting Prognosis of Hepatocellular Carcinoma

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Aims: Recently, many studies have been performed to analyze single nucleotide polymorphisms (SNPs) as a genetic marker of HCC. Synovial sarcoma translocation gene on chromosome 18-like 1(SS18L1), a calcium-responsive transactivator has been found to be associated with cancer development and progression. However, the relationships between SS18L1 and hepatocellular carcinoma (HCC) have not been studied, yet. In this study, we investigated whether single nucleotide polymorphisms (SNPs) of SS18L1 gene are associated with HCC in a Korean population.
Methods: We genotyped four SNPs (rs6142970, rs6061450, rs6142969 and rs2295207) using direct sequencing in 189 HCC patients and 194 controls. Clinicians were fulfilled detailed clinical features such as cancer size, stage of cancer and radiologic morphology. To analyze the genetic data, SNPAnalyzer, and SNPStats were used. Multiple logistic regression models (codominant, dominant, recessive and log-additive) were performed for odds ratio, 95% confidence interval, and p value. Age and gender as covariates were adjusted to obtain statistical significance.
Results: No SNPs of the SS18L1 gene were found to be associated with the risk of HCC development. Next, the relationships between SS18L1 SNPs and the clinical characteristics of HCC were investigated. rs6142970 was associated with tumor size, significantly (p= 0.034) Also, rs6061450 and rs6142969 were associated with HCC stage and tumor size. rs2295207 was associated with serum AFP level, significantly (p=0.042)
Conclusions: In conclusion, we found that SS18L1 may have a significant role in predicting the prognosis of HCC. This is the first study to demonstrate that SS18L1 polymorphisms may be associated with susceptibility to HCC in the Korean population. Further studies in different populations or other SNPs of SS18L1 will be needed.
Keywords: Hepatocellular carcinoma, Polymorphism, Prognosis

PE - 059

Downregulation of Raf-1 Kinase Inhibitory Protein as a Sorafenib Resistance Mechanism in Hepatocellular Carcinoma Cell Lines

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Aims: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and the third leading cause of cancer mortality. Sorafenib (Nexavar), the only FDA-approved systemic therapy for HCC, is a novel orally-available multikinase inhibitor blocking several crucial oncogenic signaling pathways, presented survival benefits and became the first-line drug for treatment of patients with HCC. However, sorafenib resistance is significant limiting factor to better prognosis for HCC patients. Although several mechanisms are involved in the acquired resistance to sorafenib, such as crosstalks involving PI3K/Akt and JAK/STAT pathways, hypoxia-inducible pathways, epithelial-mesenchymal transition has been reported, it is not enough to explain sorafenib resistance observed in HCC. Accordingly, our group analyzed the mechanism and key factor which cause sorafenib resistance in HCC and intend to suggest the way to overcome sorafenib resistance.
Methods: The effect of sorafenib was evaluated in HCC cell lines and patients-derived primary HCC cells. HepG2 and SNU449 were treated with sorafenib. MTS to measure cell viability and western analysis to identify alteration of signaling pathway and related molecules caused by sorafenib were performed. RKIP involvement in sorafenib resistance was corroborated by siRNA-mediated knockdown assay. These results were validated in patients-derived primary HCC cells.
Results: Sorafenib-mediated alteration of signaling pathways was examined and we identified sorafenib re-activated Ras/Raf/MEK/ERK pathway. Re-activation of Ras/Raf/MEK/ERK pathway was significantly correlated with downregulation of Raf-1 kinase inhibitory protein (RKIP). Inhibition of RKIP with siRNA induced sorafenib resistance in sensitive cell lines. Sorafenib regulated RKIP expression on post-translation level but not in transcriptional level. By increasing ubiquitination, sorafenib de-stabilized RKIP and subsequently increased turnover via ubiquitin-proteasome pathway. Combination therapy with MEK inhibitor, PD98059 and sorafenib significantly declined cell viability and proliferation, while apoptosis increased.
Conclusions: Re-activation of Ras/Raf/MEK/ERK pathway is one of the resistant mechanisms to sorafenib in HCC. Aberrant expression of RKIP caused by sorafenib might be a responsible molecule for this

re-activation. Treatment with PD98059 combined with sorafenib demonstrated the efficacy in sorafenib-resistant cells and it can suggest the possibility for preclinical study to overcome sorafenib resistance.
Keywords: Sorafenib, Resistance, RKIP, Combination therapy

Liver Cancer, Clinical

PE - 060

Histological Expression of Methionine Adenosyltransferase (MAT) I and MAT II as Post-surgical Prognostic Surrogates in Patients with Hepatitis B Virus-related Hepatocellular Carcinoma

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Aims: It has been found that methionine adenosyltransferase 1A (MAT1A) gene, encoding isoenzymes MAT I/III, is dysregulated in hepatocellular carcinoma (HCC), and reduced MAT1A expression correlates with worse HCC prognosis. The X protein of hepatitis B virus (HBV) inhibits apoptosis in HCC cells through enhancing the expression of MAT2A gene, encoding MAT II. MA1A/MAT2A switch has been severally demonstrated to be involved in hepatocarcinogenesis. We aimed to investigate prognostic implication of MAT I and MAT II protein expression in HBV-infected patients undergoing hepatic resection for HCC.

Methods: In this study, we used a tissue microarray constructed from archival surgical specimens of 166 patients with HBV-related HCC who underwent curative hepatectomy at Asan Medical Center. The tumor tissue microarray was immunohistochemically stained with primary antibodies against MAT I and MAT II. We examined pre- and post-surgical clinical factors related to MAT 1 and MAT II, using logistic regression analysis, and predictive effect of the two proteins on post-surgical recurrence and survival, using Cox proportional hazards model.

Results: Of the 166 patients, 74.1% were male with a mean age of 52.8 ± 8.7 years, 94% were Child-Pugh class A disease, and 55.4% had liver cirrhosis. In terms of histological factors, most patients had solitary tumor (93.4%) and tumors of 5cm or less (74.7%). Microvascular invasion and Edmondson grade III/IV tumors were observed in 30.7% and 66.9%, respectively of the patients. During a median follow-up of 39 months (range 5-81 months), 12 deaths and 63 recurrences had been found, where 52 recurrences occurred early within 2 years after resection. MAT I and MAT II were positively expressed in 83.7% and 87.3%, respectively of the 166 tumor tissues. MAT I expression was independently associated with male and tumors of 5 cm or less (adjusted P<0.05 for both). Expression of MAT II had a significant relationship with only serum AFP >200 ng/mL (adjusted P<0.05). Multivariate Cox regression analyses showed that MAT II expression was significantly correlated with shorter times to overall and early recurrences (hazard ratios 9.97 and 8.26, respectively; adjusted P<0.05 for both), as was not positive MAT I (hazard ratio 1.13; P=0.730). Immunopositivity for two proteins did not influence overall survival (P>0.05 for both). MAT I : MAT II activity ratio below 1.0 was observed in 12.7% of the patients, and not significantly associated with post-surgical recurrence and survival outcomes.

Conclusions: Immunohistological expression of MAT II in tumor may be helpful in predicting and monitoring tumor recurrence, especially in the early phase after hepatic resection, in patients with HBV-related HCC.

Keywords: Methionine adenosyltransferase, Hepatitis B Virus, Hepatocellular carcinoma, Recurrence

PE - 061

Living Donor Liver Transplantation for Giant Hepatic Hemangioma with Diffuse Hemangiomatosis in an Adult: A Case Report

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Aims: Giant hepatic hemagioma with multiple hemangiomatosis occupying almost whole liver is extremely rare in adults. Herein, we report a female case of rapidly growing, symptomatic giant hepatic hemangioma with diffuse hepatic hemangiomatosis who underwent orthotopic, living donor liver transplantation.

Methods Results: A 50 year old Korean woman was admitted due to dyspnea, abdominal pain and detection of huge mass showing external compression of the stomach on esophagogastroduodenoscopy in May 2015. In her past history, a hepatic hemagioma sized 10 cm in diameter and tiny hemangiomas less than 1cm were incidentally detected on healthcheck ultrasonography and CT in June 2010, but she did not follow the lesion. At this presentation, the largest vascular mass grows upto 16cm in diameter and newly appeared numerous hemangioma-like vascular lesions occupy nearly whole liver with collapsed inferior vena cava on CT, suggesting malignant vascular tumors rather than hemangiomatosis. Laboratory results showed a low platelet count (123,000/mL), microcytic hypochromic anemia (hemoglobin level of 9.3 g/dL) and prolongation of the prothrombin time of 15.9 sec (international normalised ratio, 1.31) suggesting mild Kasabach-Merritt syndrome. She denied recent or remote

estrogen administration.
Because patient's symptom forecases impending rupture of the vascular tumor, and the extensive hepatic involvement precluded surgical resection, transcatheter arterial embolization was performed to shrink the tumor. Despite possibility of malignant vascular tumor, there was no evidence of distant metastasis, and rapid growing nature of tumor leads to decision of living donor liver transplantation from her son. In Jun 2015, liver transplantation was undertaken uneventfully, and the explant liver pathology showed giant carvenous hemagioma with diffuse hepatic hemagiomatosis without evidence of malignancy. She is maintained on an immunosuppressive regimen of tacrolimus and mycophenolate in a good health until Mar 2016.
Conclusions: Liver transplantation can be a treatment option for rapidly growing hepatic giant hemangioma with diffuse hemangiomatosis in adults.
Keywords: Giant hepatic hemangioma, Living donor liver transplantation, Hepatic hemangiomatosis

PE - 062

The Clinical Implication of Anatomical Liver Resection in Patients with Hepatocellular Carcinoma in Aspect of Stemness Marker CD 133 Expression

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Aims: The positivity of stemness markers in hepatocellular carcinoma (HCC) has been reported to have a correlation with aggressive tumor factors and poor survival. Additionally, the effectiveness of anatomical resection is still debate. We analyzed the effectiveness of anatomical resection in patients with HCC in aspect of CD 133 expression.
Methods: We retrospectively reviewed the medical records of 94 patients who underwent liver resection from Mar. 2012 to Oct. 2015 by single surgeon. We investigated prognostic factors for recurrence. We analyzed effects of anatomical resection and CD 133 about recurrence.
Results: Median alpha-fetoprotein (AFP) is 10.3 (1.0-20290) ng/dl and prothrombin time induced by vitamin K absence-II (PIVKA-II) is 28 (8-37160) mAU/mL. Median tumor size is 2.5 (0.8-13) cm. 25 (26.6%) patients underwent non-anatomical resection and 69 (73.4%) patients underwent anatomical resection. CD 133 was found as positivity in 24 (26.4%) patients. Positron emission tomography (PET) positivity, satellite nodule, portal vein invasion and CD 133 positivity were significant prognostic factors for recurrence in multivariate analysis. Patients with CD 133 positive HCC showed more aggressive tumor factors and it did not show statistically significant difference. However, patients with CD 133 negative HCC showed poor disease free survival (DFS). Especially patients with CD 133 negative HCC who underwent non-anatomical resection, showed poor DFS (p=0.049).
Conclusions: Liver resection for HCC has a critical limitation like as high recurrence rate. Especially, HCC with CD 133 positivity showed aggressive tumor factors. Although our study has some limitations like as small number of samples and short follow-up duration and then cannot show statistically significant difference, Anatomical resection may decrease recurrence rate, especially in patients with CD 133 positive HCC.
Keywords: Hepatocellular carcinoma, Anatomical resection, Recurrence, CD133

PE - 063

Incidence of Hepatocellular Carcinoma in Subjects with Hepatitis B Virus Positive in Korean National Liver Cancer Screening Program

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Aims: To optimize efficacy of National Liver Cancer Screening Program (NLCSP) for subjects with hepatitis B surface antigen (HBsAg) positive, it is crucial to know the incidence of hepatocellular carcinoma (HCC) development and its predisposing factors in the program.
Methods: From January 2010 to December 2014, all the HBsAg positive participants who received at least two or more abdominal ultrasonography under NLCSP were retrospectively enrolled in a single tertiary hospital. Annual incidence of HBV-related HCC was calculated and related clinical factors were investigated.
Results: During 5 years, 541 subjects were enrolled. Mean age was 53 years old and 310 (57.3%) were male. Most subjects (86.5%) were patients of current hospital. Two hundred ninety two subjects (54%) were receiving antiviral agents at the moment. Liver cirrhosis (LC) was diagnosed in 212 (39.2%) by ultrasonography or upper endoscopy. Esophageal varices were found in 63 (14.8%). Total bilirubin, albumin, platelets, and aminotransferases were normal in most subjects. HBV DNA were less than 2,000 IU/mL in 356 subjects (79.6%). Mean follow-up time was 2.4 years and 16 new HCCs were diagnosed. Annual incidence of HBV-related HCCs were 980 per 100,000 patient year (1% per year). Subjects more than 60 years old (2.2% per year) had higher risk of HCC development than those under 60 years (0.6% per year, P<0.005 by Log Rank test). Presence of LC (2.2% per year) also showed higher risk of HCC than LC-free state (0.2% per year, P<0.0001 by Log Rank test). In cirrhotic patients older than 60 years old, the incidence increased up to 3.8% per year.
Conclusions: Despite of high rate of antiviral therapy, incidence of HBV-related HCC is not low in participant of NLCSP in Korea. Old age and presence of liver cirrhosis are associated with higher risk of HCC development.
Keywords: Hepatocellular carcinoma, Chronic hepatitis B, Screening

PE - 064

Risk of Hepatocellular Carcinoma Development Is Much Higher in Korean Patients with Chronic Hepatitis B than in Taiwanese

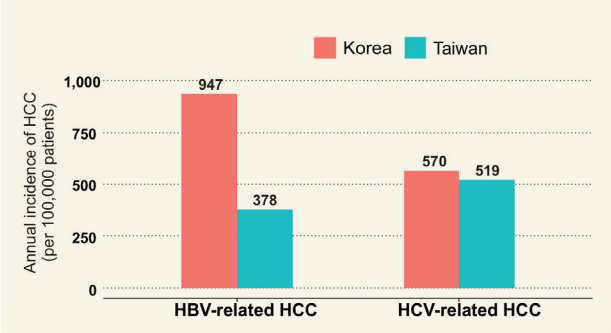

Figure 1. Annual incidence of hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis B or C. Data were obtained from national cancer reports and large-scale prevalence studies of viral hepatitis in Korea and Taiwan. The annual incidence of HBV- or HCV-related HCC per 100,000 patients (40 to 79 years of age) with chronic hepatitis B or C is shown.

Jae-Jun Shim, Tae-Woong Choi, Chi Hyuck Oh, Soyung Park, Yu Jin Um, Byung-Ho Kim*

Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Republic of Korea

Aims: Asians have a higher risk of hepatocellular carcinoma (HCC) development than Caucasians. However, the risk of HCC was not compared among Asian countries.

Methods: Population data, prevalence of chronic hepatitis B or C, and annual number of hepatitis B virus (HBV) - or hepatitis C virus (HCV) - related HCC cases (40-79 years of age) were acquired from publicly available data. The incidence of HCC among patients with chronic viral hepatitis were calculated according to age groups

Results: The risk of HBV-related HCC in Koreans was more than twice that in Taiwanese. The annual incidence of HCC was 947 per 100,000 HBsAg-positive patients in 2005. This was equivalent to 1 HCC occurrence for every 106 patients with chronic hepatitis B (CHB) per year. From 2005 to 2011, the annual incidence in Korea did not change; the average was 906 per 100,000 persons (0.91%/year). In Taiwan, the incidence was 378 per 100,000 patients per year in 2002. One HCC was diagnosed for every 265 patients with CHB. The incidence among young adults (40-49 years of age) was compared because most HCCs that develop in individuals in this age group are HBV-related. The incidence was 495 and 155 per 100,000 patients with CHB in Korea and Taiwan, respectively. The mortality rate due to HBV-related HCC was 434 and 136 per 100,000 patients in Korea and Taiwan, respectively. However, the incidence of HCV-related HCC was similar in the two countries; 570 and 519 per 100,000 patients with chronic hepatitis C in Korea and Taiwan, respectively.

Conclusions: The risk of HCC is much higher in Korean patients with CHB than in Taiwanese, however the risk is similar among chronic hepatitis C.

Keywords: Chronic hepatitis B, Hepatocellular carcinoma, Incidence, Korea

PE - 065

Application of REACH-B Model to Predict Hepatocellular Carcinoma Risk in Patients with Chronic Hepatitis B under Oral Antiviral Therapy

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Aims: REACH-B is a simple scoring system to predict HCC risk in non-cirrhotic patients with chronic hepatitis B (CHB). However, it is not known whether the model can accurately predict HCC risk in patients under long-term antiviral therapy. This study aimed to validate modified REACH-B model to predict HCC risk in patients receiving entecavir.

Methods: From 2007 to 2013, total 136 naïve patients (40 to 70 years of age) with CHB who had been treated for more than 6 months were retrospectively collected. None of them had liver cirrhosis. We hypothesized that HCC risk remains unchanged during the first two year and decrease thereafter. Two-year HCC risk was calculated from baseline data before antiviral therapy and the remaining 3-year risk was calculated from improved parameters following 2-year antiviral therapy.

Results: Median age of patients was 49 years. HBeAg positive CHB were 77 (56.6%). Median ALT was 102 U/L. Baseline serum HBV DNA level was 7.51 log10 copies/mL. The patients were observed for total 507.5 years. The 5-year HCC risk of non-treated patients was predicted as 7.36%. It was equivalent to annual incidence of 1,472 per 100,000 persons with CHB. If they were treated, the 5-year HCC risk was dramatically decreased to 2.48%. Annual incidence was 496 per 100,000 persons with CHB. During actual follow-up period, two patients developed HCC. The incidence was 394 per 100,000 person year and 5-year cumulative incidence was estimated to 1.97%. There was no difference between predicted and actual incidence of HCC (P = 0.907 by Log Rank test). Actual and predicted incidence following antiviral therapy decreased as compared with that of non-treatment, however, the difference did not meet statistically significance (P = 0.176 by Log Rank test).

Conclusions: Modified REACH-B model can predict 5-year risk of HCC in patients with CHB under long-term antiviral therapy.

Keywords: Hepatocellular carcinoma, Chronic hepatitis B, Prediction, Antiviral therapy

PE - 066

Obesity and the Risk of Mortality in Newly-diagnosed Hepatocellular Carcinoma

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Aims: The influence of body mass index (BMI) on the outcome of patients with hepatocellular carcinoma (HCC) is unclear, particularly in a hepatitis B virus endemic area. We investigated whether the influence of BMI on survival of newly-diagnosed HCC patients.

Methods: A total of 3,104 patients with HCC were analyzed. Patients were stratified into four groups: underweight (<18.5 kg/m^2), normal

weight (18.5-22.9 kg/m^2), overweight (23.0-24.9 kg/m^2), and obesity (≥ 25.0 kg/m^2).

Results: The median survival was significantly different according to the BMI: 2.3, 3.8, 4.2 and 5.2 years for underweight, normal weight, overweight and obesity, respectively ($p < 0.001$). Compared to normal weight, underweight showed higher risk for mortality [Hazard ratio (HR), 95% confidence interval (CI): 1.37, 1.04-1.82, $p = 0.025$], overweight showed marginal association with mortality (HR, 95% CI: 0.90, 0.80-1.01, $p = 0.097$), and obesity showed lower risk for mortality (HR, 95% CI: 0.82, 0.73-0.91, $p < 0.001$). However, tumor stage and liver function were favorable in overweight/obese patients than normal weight patients, while it was worse in underweight patients. In multiple-regression model, there was no independent association between BMI and patient survival.

Conclusions: The survival of obese patients was longer than normal weight patients while it was shorter in underweight patients. However, the observed survival difference was mediated by different clinical characteristics at presentation, and BMI did not independently influenced overall survival of HCC patients.

Keywords: Hepatocellular carcinoma, Survival, Body mass index, Obesity

PE - 067

Primary Prophylaxis for Variceal Bleeding Improves Survival of Patients with Newly-diagnosed Hepatocellular Carcinoma

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Aims: We evaluated the impact of primary variceal bleeding prophylaxis on long-term outcomes of patients newly-diagnosed with hepatocellular carcinoma (HCC).

Methods: A retrospective cohort of 898 patients newly-diagnosed with HCC without a history of variceal bleeding [age: 57.4 ± 10.4, males = 718 (80.0%)] were analyzed for new onset variceal bleeding during follow-up. The effect of primary prophylaxis for variceal bleeding on overall survival was assessed.

Results: Variceal bleeding occurred in 72 patients (8.0%) during follow-up. The presence of portal vein thrombosis [hazard ratio (HR), 3.90; 95% confidence interval (CI), 2.09-7.30; $p < 0.001$] and presence of the red color sign or ≥ grade 2 varices at index endoscopy (HR, 7.64; 95% CI, 4.56-12.8; $p < 0.001$) were independent risk factors for variceal bleeding. The occurrence of variceal bleeding was an independent risk factor for mortality (HR, 1.39; 95% CI, 1.06-1.82; $p = 0.015$). At baseline, 138 patients were indicated for primary prophylaxis and 71% received primary prophylaxis, whereas 29% did not. Primary prophylaxis for variceal bleeding for indicated patients was marginally associated with a reduced risk for variceal bleeding (HR, 0.49; 95% CI, 0.21-1.13; $p = 0.096$) and was associated with reduced risk for overall mortality (HR, 0.54; 95% CI, 0.33-0.88; $p = 0.014$).

Conclusions: Variceal bleeding increased the risk of overall mortality and primary prophylaxis of variceal bleeding reduced the risk for mortality for indicated patients. These findings suggest that screening and providing primary prophylaxis for indicated patients should be done for patients newly-diagnosed with HCC.

Keywords: Hepatocellular carcinoma, Varix, Bleeding, Prevention

PE - 068

Clinical Profile, Prognostic Factors, and Survival of Patients with Hepatocellular Carcinoma in Two Philippine Tertiary Centers

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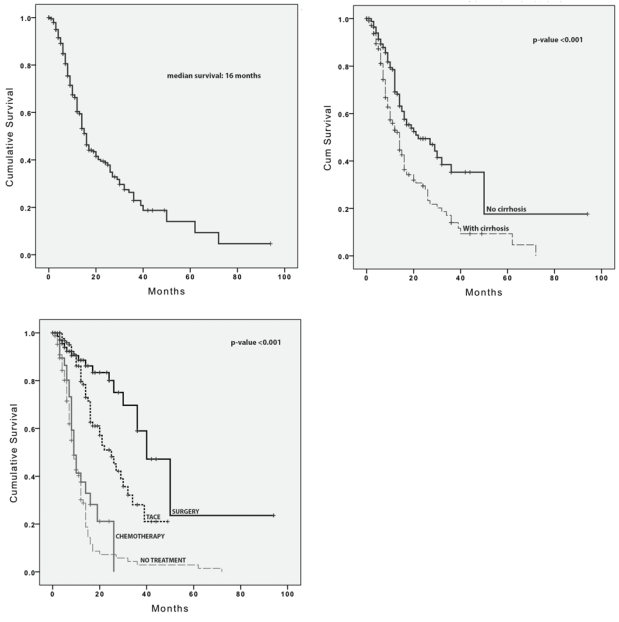
Aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death in the Philippines and in the world. Most burden of disease is seen in developing countries, with highest incidence reported in hyperendemic regions for Hepatitis B infection. This study identified the prognostic factors and overall survival of patients with HCC.

Methods: This retrospective study included adult patients diagnosed with HCC at two Philippine tertiary hospitals from 2007 to 2014. Demographics, tumor characteristics, risk factors, and treatment outcomes were retrieved through review of medical records. STATA v12 was used to perform univariate and multivariate logistic regression.



Overall survival was also determined.
Results: Four hundred twenty-nine patients, with a mean age of 59.6+13.2 years (M:F ratio 3.6:1), were included. Almost half (49%) had advanced HCC on diagnosis. Fifty-two percent had documented HBV infection, and liver cirrhosis was present in 56%. Furthermore, tumors were usually solitary (59%). Only 57% were able to proceed with treatment. Significant predictors of survival were surgical resection (OR 0.12, p-value <0.001), Child Turcotte Pugh (CTP) classification (CTP B: OR 2.26, p-value 0.024; CTP C: OR 5.54, p-value 0.013), liver cirrhosis (OR 2.56, p-value 0.007), and portal vein thrombosis (PVT) (OR 2.68, p-value 0.035). Forty-two percent of the patients died, with a median overall survival of 16 months.
Conclusions: CTP classification, liver cirrhosis, PVT, and surgical resection were identified as significant predictors of survival in HCC. Due to innate limitations of retrospective studies, a prospective study will help in determination of association between severity of disease and treatment outcomes.
Keywords: Hepatocellular Carcinoma, HCC, Prognostic Factors, Survival

PE - 069

Therapeutic Priority for a Solitary Large Hepatocellular Carcinoma in South Korea: An Analysis of Nationwide Cancer Registry Database

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Aims: We compared overall survival (OS) of patients with a solitary large (>5cm) hepatocellular carcinoma (HCC) treated surgically or by transarterial chemoembolization (TACE).
Methods: The archived records of HCC patients registered at Korean Central Cancer Registry from January 2003 through December, 2005 (registry A, n=4,520) or from January, 2008 through December, 2010 (registry B, n=4,596) were retrospectively analyzed. In each registry, 578 and 315 patients had a single large HCC, respectively. Of the 578 patients, 442 (cohort A) underwent surgery (n=96) or TACE (n=346). Of the 315 patients, 253 (cohort B) underwent surgery (n=110) or TACE (n=143). Cohort C (n=695) was developed using the two cohorts, and 206 and 489 patients received surgery and TACE, respectively. The OSs in each cohort were compared between two treatment groups with or without propensity score matching.
Results: In cohort C, median tumor size was 7.6 cm (range, 5.1-23 cm). Median follow-up duration after treatment was 31.3 months (range, 1-107.9 months). Cumulative OS rates at 1-, 3-, and 5-years were significantly higher in surgical group than TACE group (89.3%, 67.4%, and 58.0% vs. 67.7%, 38.2%, and 27.2%, respectively, p<0.001). This was similar in analyses for cohort A (p<0.001) and B (p<0.001). TACE (HR 2.18, p<0.001), serum albumin (HR 0.77, p=0.015), or tumor size (HR 1.06, p<0.001) were independent predictors of post-treatment mortality. After propensity score matching in three cohorts, the cumulative OS in surgical groups were significantly greater than in TACE groups, respectively (p-values for all <0.05).
Conclusions: OS was better in surgery group than TACE group for a solitary large HCC.
Keywords: Hepatocellular carcinoma, Surgery, Transarterial chemoembolization, Barcelona Clinic Liver Cancer

PE - 070

Epidemiology and Prognosis of Hepatocellular Carcinoma in Mongolia

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Aims: Hepatocellular carcinoma (HCC) is the most common cancer in Mongolia, with an occurrence of 115 cases per 100,000 people. We aimed to investigate the clinical features, therapeutic modalities, overall survival, and prognostic factors for Mongolian patients with HCC.
Methods: 195 patients with HCC were consecutively enrolled in our study. Diagnosis of HCC was made according to the EASL guidelines.
Results: The mean age (108 males and 87 females) was 61.7 years. A large proportion of patients (n=165, 84.6%) had underlying liver cirrhosis. The most common etiology for HCC was HBV infection (n=67, 34.4%), followed by HCV infection (n=89, 45.6%). The mean tumor diameter was 6.0 ± 2.6 cm. Only 29 (14.9%) patients had a single lesion, while 39 (20.0%) had >3 lesions. Extra hepatic metastasis to the lung (n=23), bone (n=10), and lymph node (n=3) was detected in 36 (18.5%) patients. The mean serum AFP level was 196.0 ng/ml. Most patients had advanced HCC; 88 (45.1%) in stage III and 57 (29.2%) in stage IV. Surgical resection was performed in 27 (13.8%) patients, RFA in 23 (11.8%), and TACE in 107 (54.9%). In 38 (19.5%) patients with distant metastasis or poor liver function, the best supportive care was provided. When all the patients were categorized as 'treated' (n=156) and 'not treated' (n=39), the 3 year survival was significantly lower in the 'not treated' group than in the 'treated' group (11% vs 0%, P<0.001). Tumor diameter (<3 cm vs ≥3 cm), extra hepatic metastasis, TNM stage (I/II vs. III/IV), and treatment (or supportive care) were selected as independent predictors for survival.
Conclusions: The number of patients diagnosed with an advanced stage of HCC in Mongolia is relatively high, and the survival rate of these patients is lower compared to other countries due to limited treatment modalities.
Keywords: HCC, Mongolia, Cancer

PE - 071

The Possibility of Radiotherapy for Downstaging before Living Donor Liver Transplantation for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Aims: Advanced HCC with portal vein tumor thrombus (PVTT) patients are excluded for liver transplantation (LT), according to the Milan criteria. But after the development of conformal RT, there have been several trials on RT as a bridge or downstaging management approach to LT. The purpose of our study is to evaluate the value of living donor liver transplantation (LDLT) following RT in PVTT patients.
Methods: This study took place between May 1996 and March 2013; a, total of 1360 patients were treated by LT in our institution, and 5 of those recipients had RT due to PVTT. To confirm the value of LDLT following RT in PVTT, we did a propensity-matched study retrospectively.
Results: There were no statistically significant differences in the clinical characteristics of the two groups. All LT was done by LDLT with duct to duct anastomosis and the mean operation time was 588 minutes. During the follow-up periods, in the LDLT following RT group, two recipients exhibited disease progression, but in the RT alone group, all patients had tumor ingrowths or either intra- or extra-hepatic metastasis. The OS for the LDLT following RT group was 1055 days and that of the RT alone group was 367 days, and there was a statistically significant difference.
Conclusions: LDLT following RT can be the treatment of choice for PVTT in select patients and when bile duct anastomosis was performed in RT recipients, a hepaticojejunostomy was recommended to prevent biliary complications.
Keywords: Liver transplantation, Hepatocellular carcinoma, Portal vein tumor thrombus, Downstaging

PE - 072

Macro-vascular Invasion of Hepatocellular Carcinoma Is not an Absolute Contraindication for Living Donor Liver Transplantation

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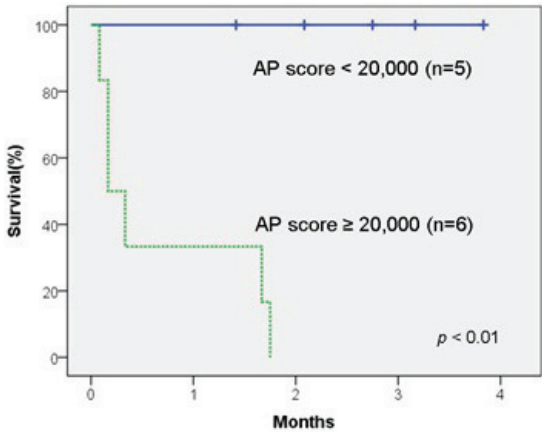
Aims: In spite of expansion of indication for advanced hepatocellular carcinoma (HCC), the portal vein tumor thrombosis (PVTT) has been accepted as an absolute contraindication for liver transplantation. However, we experienced unexpectedly good prognosis in selected cases with pre-transplant PVTT. In this study, we tried to identify the prognostic factors after living donor liver transplantation (LDLT) for HCC with major PVTT.
Methods: Between January 2009 and December 2013, 282 patients underwent living donor LT (LDLT) for HCC at our institution. Among them, 11 patients (3.9%) with major PVTT diagnosed before transplantation were retrospectively reviewed.
Results: The duration of follow-up was more than 2 years in all patients. HCC recurrence occurred in 6 patients (54.5%) after LDLT.



One-year, 3-year, and 5-year recurrence-free survival was 63.6%, 42.4%, and 42.4%, respectively. One-year, 3-year, and 5-year overall survival was 72.7%, 63.6%, and 63.6%, respectively. Main PV invasion, high value of multiplication of AFP and PIVKA-II (AP score, ≥ 20,000), large original tumor (> 7cm) were significant risk factors for HCC recurrence after LDLT in pre-transplant major PVTT. There was no recurrence in 5 patients with low AP score (< 2,000).
Conclusions: If pre-transplant PVTT is not to exceed main PV and AP score is less than 20,000, we can consider LDLT as a curative treatment option. [figure1]
Keywords: Hepatic bile salt, Bile acid transporter, Transporter expression, Warm ischemic injury

PE - 073

Minimal Incision Right Donor Hepatectomy: A Single Center Experience

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Aims: Minimizing the risk to organ donors is one of the reasons for the development of a less invasive technique. However, during the learning curve, donor morbidty and poorer graft function may be increased. This could be prevented with a step up approach, starting with a minimal incision, and with additional experiences, advancing to a total laparoscopic. The aim of this study was to evaluate our experience in minimal incision donor hepatectomy.
Methods: Between January 1999 and February 2014, One thousands LDLT were performed at Seoul National University Hospital. Among them, 39 donors (3.9%) underwent minimal incision donor hepatectomy (37 right hemihepatectomy and 2 left lateral sectionectomy). We retrospectively analyze 37 minimal incision right hepatectomy, including Gasless Hand-assisted (GHA), Hybrid and Hand-assisted (HA) procedures.
Results: There were 29 females and 8 males out of 37 donors, with the mean age of 25.32 ± 6.11 years old and median BMI 26.62 (17.16 - 30.26) kg/m2. Twenty patients (51.3%) had a transverse incision and 19 patients (48.7%) had an upper midline incision. Hybrid procedure was associated with a least EBL (223.50 ± 141.66), compared to GHA (282.5 ± 92,69) and HA (536.88 ± 92) [p =0.007].

There was no statistically significant difference in the length of stay of all techniques. Further analysis on the parenchymal transection technique, reveal a statistically significant difference between open and hand-assisted transection method, in terms of EBL (249.72 ± 122.77 vs. 536.88 ± 299.92, p =0.045) and Operating time (332.89 ± 106.29 vs 436.25 ±154.40, p=0.027). Intra operative and post-operative complications were found in 4 (10.8%) and 16 (43.2%) donor, respectively.

Conclusions: Hybrid procedure of minimal incision right hepatectomy with laparoscopic liver mobilization continue with open liver parenchymal transection, is a safe and visible option in high volume transplantation center and should be taken into consideration when consulting a future donor.

Keywords: Living donor liver transplantationi, Right donor hepatectomy, Minimal incision

PE - 074

Validation of the MORE Score Model Predicting Survival of Patients with Recurrent or Progressive Hepatocellular Carcinoma

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Aims: There has been no prognostic model to evaluate the survival of patients with hepatocellular carcinoma who experience disease recurrence or progression after initial treatment. A model predicting survival of patients with recurrent or progressive hepatocellular carcinoma (MORE score) has recently been developed using clinical parameters, tumor characteristics, initial treatment modality, and response to treatment, and was validated in a single patient cohort. We tried to evaluate the performance of this novel model by applying it to a different prospectively collected patient cohort.

Methods: Of 1,010 patients who were newly diagnosed with and who had undergone initial treatment for hepatocellular carcinoma at the National Cancer Center, Korea, between January 2010 and December 2013, 460 had documented disease recurrence or progression. Clinical data at the time of recurrence or progression were collected and reviewed. A newly developed prognostic model, the MORE score, was used to calculate the survival probabilities of these patients at the time of recurrence or disease progression, and its performance was evaluated using C-statistics for discrimination ability and χ^2 statistics for fitting ability.

Results: The median age was 58.5 years (range, 17-84 years), and the predominant etiology for hepatocellular carcinoma was hepatitis B virus infection (74.3%). The most commonly used initial treatment was chemo-embolization (64.6%), followed by resection (19.6%). The median time to progression after initial treatment was 4.9 months. C-statistics of the MORE score for 1-, 3-, and 5-year survival were 0.892 (95% confidence interval: 0.865-0.919), 0.842 (0.816-0.868) and 0.829 (0.824-0.854) respectively; χ^2 statistics showed corresponding values of 9.651, 17.170, and 19.629 for 1-, 3-, and 5-year survival.

Conclusions: The MORE score was validated using a different patient cohort that was collected prospectively. The model showed excellent discrimination ability and correctly predicted the survival of the patients, especially at 1 year. This novel model should be useful in real-world clinical practice in communicating with patients and planning subsequent treatment.

Keywords: Hepatocellular carcinoma, Prognosis, Survival, Model, Validation

PE - 075

Colonoscopic Cyanoacrylate Injection of Bleeding Ileal Varices in a Patient with Hepatocellular Carcinoma

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Aims: Ectopic varices are rare and can occur in approximately 1-3% of cirrhotics - with small intestinal varices occurring in 17-18% of these patients. Due to its rarity, there is still no current standard of care for the treatment of ileal varices. We present a case in which bleeding terminal ileal varices was successfully controlled by colonoscopic cyanoacrylate injection.

Methods: A 34 year-old male diagnosed with chronic hepatitis B was admitted due to hematochezia. Physical examination revealed a non-tender right upper quadrant mass. Laboratories showed severe anemia, deranged liver biochemical tests, and a markedly elevated alpha feto protein. Triphasic abdominal CT scan showed an arterially-enhancing mass with rapid wash out occupying and enlarging the left liver lobe.

Results: On admission, he was transfused with 3 units packed red blood cells until esophagogastroduodenoscopy (EGD) and colonoscopy were performed. On EGD, four columns of engorged vessels were noted and 3 bands were deployed. No gastric or duodenal varices were found. On colonoscopy, an engorged vessel with nipple sign was noted 8-12 cm from the ileocecal valve. Intraluminal injection of N-butyl-2-cyanoacrylate (Histoacryl) on the ileal varices was performed without complications. Second-look colonoscopy showed sclerosed ileal vessels without any signs of active bleeding. CT-angiogram revealed absence of any vascular abnormalities or contrast extravasation. The patient was then primed for TIPS and palliative chemotherapy, however on the 9th day post-histoacryl injection, the patient expired due to respiratory failure.

Conclusions: Ectopic varices are uncommon and the optimal treatment remains to be a challenge. Colonoscopic injection sclerotherapy is a promising option for control of terminal ileal variceal bleeding even in poor risk patients presenting with massive hemorrhage.

Keywords: Ileal varices, Cyanoacrylate, Cirrhosis, Hepatocellular carcinoma

PE - 076

Detection of Hepatocellular Carcinoma at Advanced Stages in Patients with Chronic Hepatitis B Who Underwent

Regular Surveillance: Predictors for Detection Failure

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Aims: Some patients in clinical practice are diagnosed at late stages in spite of routine surveillance with ultrasound and alpha-fetoprotein (AFP) every 6 months. The aim of our study was to determine the predictors for detection failure of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) who underwent regular surveillance.

Methods: Patients with CHB and well-preserved liver function, who underwent routine surveillance with ultrasound and AFP every 6 months, were enrolled. Cox regression analysis was used to identify predictors for detection failure, defined as HCC diagnosed beyond Barcelona Clinic Liver Cancer (BCLC) stage B.

Results: During the mean follow-up of 1.6 (0.5-8.8) years, 3,528 chronic HBV patients had routine surveillance. The mean age was 54.2 years and 2.173 (61.6%) patients were men. Of 154 patients with HCC, 29 (18.8%) were detected beyond BCLC stage B. On multivariate analysis incorporating liver cirrhosis on ultrasound, liver cirrhosis (hazard ratio [HR] 3.96; 95 % confi dence interval [CI]: 1.55 - 10.09), AFP >20 ng/mL (HR 7.52, 95 % CI: 3.20 - 17.66), and diabetes mellitus (HR 2.91, 95 % CI: 1.28 - 6.64) were identified as independent predictors of detection failure. On the other model with liver stiffness (LS) value, predictors of detection failure included LS value > 12kPa (HR 9.53, 95 % CI: 1.80 - 50.53) and AFP >20 ng/mL (HR 5.61, 95 % CI: 1.76 - 17.84).

Conclusions: Detection failure of HCC was common reflecting the imperfectness of current surveillance method. In CHB patients with liver cirrhosis and/or high LS value, or high AFP, other better surveillance strategies should be considered.

Keywords: Hepatocellular carcinoma, Ultrasound, Alphafetoprotein, Chronic hepatitis B

PE - 077

The Association between the State of Lipiodol Uptake after TACE and Recurrence of HCC

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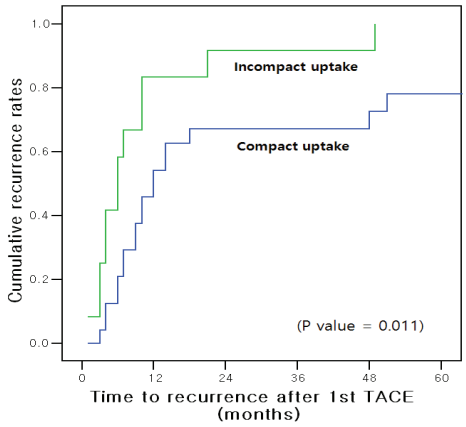
Aims: Transarterial chemoembolization (TACE) has regarded as one of the major therapies for Hepatocellular carcinoma (HCC). However, the frequent recurrence after TACE has been a major limitation of HCC treatment. We evaluated whether compact or incompact lipiodol uptake in tumors after first TACE affects the rates and patterns of recurrence.

Methods: We retrospectively analyzed the HCC patients who underwent first TACE at Seoul Paik Hospital from January 2000 to March 2016. Only HCC patients with the size ≤ 5 cm and the number less than 3 who were followed up at least more than 6 months after TACE were included in this study. A total of 36 HCC patients (M:F=26:10; Age: 65.3 ± 9.1 years; 21 HBV, 11 HCV, 2 alcohol, 2 unknown; Child-Pugh Class 29 A, 6 B) were subjected. We analyzed relationship between the state of lipiodol uptake and the rates and patterns of first detected recurrence during follow-up.

Results: On an abdominal CT performed one month after first TACE, compact lipiodol uptake was noted in 24 patients and incompact lipiodol uptake was seen in 12 patients. In the compact lipiodol uptake group, regarding recurrence patterns, marginal recurrence, intrahepatic recurrence as new lesion, and both of them were 21.1%, 68.4%, and 10.5%, respectively, while in incompact uptake group, 50.5%, 41.7%, and 8.3%, respectively. The cumulative recurrence rate of HCC at 1, 2, and 3 years after 1st TACE were significantly lower in compact uptake group than in incompact uptake (54.2%, 67.2%, and 67.2% vs. 83.3%, 91.7%, and 91.7%, respectively, P=0.011). The cumulative rates of marginal recurrence of HCC was significantly higher in the incompact uptake group (P=0.008).

Conclusions: The patients with incompact lipiodol uptake after TACE showed significant higher rates of recurrence. Therefore, further management for HCC or short term follow up should be considered in these patients.



Keywords: Hepatocellular carcinoma, Lipiodol uptake, Recurrence, Transarterial chemoembolization

PE - 078

Influence of Alcohol Intake on the Stage and Outcomes of Hepatocellular Carcinoma

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Aims: Alcohol, a group 1 carcinogen, is a well-known risk factor for hepatocellular carcinoma (HCC). We investigated whether lifetime alcohol intake would be associated with the tumor characteristics or prognosis of HCC.

Methods: Of 826 patients initially diagnosed with HCC at a single

institution between January 2007 and December 2009, 651 patients with available documented history of alcohol intake were enrolled. The total amount of alcohol intake was calculated based on written questionnaires at the first clinic visit. Patients were categorized into 4 groups according to the etiology: Hepatitis B virus (HBV)-related (HBV+, n=462), hepatitis C virus (HCV)-related (HCV+, n=55), both HBV and HCV-related (HBV+/HCV+, n=21), and non-virus-related (HBV-/HCV-, n=110). Clinical features and prognosis were analyzed according to the presence or absence of alcohol intake or the amount of alcohol intake.

Results: Of 651 patients, 431 had a history of drinking alcohol (alcohol group) and 220 had no history of drinking alcohol (non-alcohol group). There were no significant differences between the alcohol and non-alcohol groups in terms of tumor size, number of nodules, tumor stage, Child-Pugh class, or overall survival. Significant differences in tumor stage were observed between alcohol and non-alcohol groups for the HBV+ group in subgroup analysis (p=0.038): stage I (5.1% vs. 11.5%), stage II (31.3% vs. 31.5%), stage III (24.2% vs. 26.7%), stage IVa (24.6% vs. 15.8%), and stage IVb (14.8% vs. 14.6%). There were no other significant differences between the alcohol and non-alcohol groups across etiologies for HCC. The amount of alcohol intake also did not affect the tumor characteristics or prognosis of HCC.

Conclusions: In this cohort, the non-alcohol group of HBV-related HCC patients tended to have more stage I and less stage IVa diagnosis. However, there was no significant difference in tumor characteristics, Child-Pugh class, or overall survival according to the history or amount of alcohol reported in the questionnaire.

Keywords: Hepatocellular carcinoma, Alcohol

PE - 079

A Case of Primary Angiosarcoma with Diffuse Hepatic Involvement

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Aims: In adults, primary tumors of the liver arising from the vascular elements of mesenchymal tissues include hemangioma and rare malignant tumors such as epithelioid hemangioendothelioma or angiosarcoma. Although these tumors appear usually as solitary or multiple nodules, they rarely present with diffuse nodular lesions. Here, we report a case of primary hepatic angiosarcoma in whom diffuse infiltrative lesions were diagnosed by transjugular liver biopsy.

Methods Results: A 60-year-old woman with a history of hypertension visited emergency department complaining of pitting edema and abdominal discomfort. The laboratory examination showed anemia(hemoglobin 9.7g/dL), mild elevation of alkaline phosphatase 311U/L, gamma-glutamyltransferase 173U/L, total bilirubin1.92mg/dl, and prothrombine time (INR) 1.38. Echocardiography showed normal ejection fraction and no chamber enlargement. Liver dynamic computed tomography (CT) showed multifocal high-density irregular lesions scattered on precontrast image, which were enhanced on delayed image. Liver dynamic magnetic resonance imaging (MRI) showed diffuse infiltrative arterial enhancing masses with gradual centripetal enhancement involving both hemilivers, suggesting diffuse hepatic hemangiomatosis or epithelioid hemangioendothelioma and angiosarcoma. Initial tranjugular liver biopsy yielded insufficient specimen for proper histopathologic diagnosis. She complained of right flank pain 9 days after liver biopsy. Her blood pressure was 88/56 mmHg and hemoglobin was 6.6 g/dL. Spontaneous rupture and hemoperitoneum was detected on the follow up CT scan. Emergent hepatic artery embolization was performed. In consideration of liver transplantation for the curative treatment, repeat transjugular liver biopsy was performed to exclude malignancy. Pathologic examination showed malignant vascular tumors, consistent with angiosarcoma. Twenty four days following repeat liver biopsy, the patient expired due to progressive hepatic failure.

Conclusions: Primary vascular tumors of the liver can appear diffuse infiltrative masses with gradual centripetal enhancement involving the entire liver on CT or MRI scan. Although liver biopsy poses a risk of bleeding especially in vascular tumors, pathologic confirmation is needed to identify the diagnosis between diffuse hepatic hemangiomatosis, epithelioid hemangioendotheliomas, and angiosarcomas. Transjugular liver biopsy is relatively safe, and can assist in the conformatory diagnosis of hepatic vascular tumors.

Keywords: Angiosarcoma, Transjugular liver biopsy

PE - 080

Development of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B under Oral Antiviral Therapy

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Aims: Risk for hepatocellular carcinoma (HCC) development decreases but not completely disappears by long-term use of nucleos(t)ide analogues in patients with chronic hepatitis B (CHB). The aim of this study was to investigate incidence of HCC in CHB patients under antiviral therapy and to reveal clinical parameters related with HCC development.

Methods: We collected clinical data retrospectively from 364 consecutive naïve patients with CHB (40 to 70 years of age), who received entecavir for more than 6 months from January 1, 2007 to December 31, 2013. Incidence of HCC according to various clinical parameters including presence of liver cirrhosis was estimated. Kaplan-Meyer analysis and a multivariable Cox proportional hazards model were used for analysis.

Results: Median age of patients was 51 years. Among the patients, 228 (62.6%) had liver cirrhosis, and 338 (92.9%) achieved complete virological response. Median ALT was 74 U/L and serum HBV DNA level was 6.79 log10 copies/mL. Total observation time of all patients was 1,293 years (mean 3.6 years per patient). During the period, 46 patients (12.6%) developed HCC. In univariate analysis, presence

of liver cirrhosis, old age more than 50 years, low albumin (< 3.8 g/dL), and low platelet counts (< 120,000/mm3) were associated with higher risk of HCC development. In multivariate analysis, only presence of liver cirrhosis at the starting time of antiviral therapy was significantly associated with higher risk of HCC development (hazard ratio 6.9; 95% confidence interval [CI], 1.6-30.8) Annual incidence of HCC between cirrhotic and non-cirrhotic patients was 5.6% and 0.4% per year, respectively (P<0.001 by Log Rank test).

Conclusions: Once CHB progressed to liver cirrhosis, risk for HCC development is unacceptably high despite of long-term antiviral therapy. We should consider earlier initiation of antiviral therapy before too late.

Keywords: Hepatocellular carcinoma, Chronic hepatitis B, Antiviral therapy, Entecavir

PE - 081

The Clinical Outcomes of Advanced HCC Patients Received Systemic Cytotoxic Chemotherapy after Sorefenib Failure

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Aims: The role of systemic cytotoxic chemotherapy has not to be elucidated in patients with advanced hepatocellular carcinoma (HCC) after sorafenib failure. We analyzed clinical outcomes of patients who received systemic cytotoxic chemotherapy after sorafenib failure.

Methods: Between 2007 and 2015, there were 47 advanced HCC patients treated with systemic chemotherapy after sorafenib at Korea University Guro hospital. The most common regimen was doxorubicin, cisplatin and capecitabine containing regimen (87.2%). Data for each patient was collected retrospectively including demographic, laboratory, clinical, treatment and survival data. Tumor response was assessed by RECIST version 1.1. Overall survival and progression free survival were analyzed through Kaplan-Meier curve.

Results: In baseline characteristics, chronic hepatitis B (76.6%) was main etiologic factor in development of HCC. ECOG performance status 0 and 1 were 29.8% and 68.1%. 85.4% of patients were Child-Pugh class A. 40 patients (85.4%) had distant metastasis and lung was the most frequent metastatic organ (26 patients). Patients with portal vein invasion were 20 (42.5%). During follow up, 33 patients were died and overall median survival was 9.8 months (95% CI, 6.0-13.6). The median progression-free survival was 6.0 months (95% CI, 4.6-7.4). In analysis of best response rate, no patient had CR, 10 patients had PR (21.3%), 14 patients had SD (29.8%), and 16 patients had PD (34.0%). The overall objective response rate was 21.3% and the disease control rate was 51.1%.

Conclusions: In this study, systemic cytotoxic chemotherapy showed favorable response. Therefore, systemic cytotoxic chemotherapy could be considered in patients with hepatocellular carcinoma after sorafenib failure in present situation that there is no option for second-line therapy.

Keywords: Chemotherapy, HCC, Sorafenib

PE - 082

Prediction of Response to Sorafenib in Hepatocellular Carcinoma: A Marker Panel by Multiple Reaction Monitoring-mass Spectrometry

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Aims: Sorafenib is the only standard treatment for advanced hepatocellular carcinoma (HCC), but it provides modest survival benefits over placebo, necessitating predictive biomarkers of the response to sorafenib.

Methods: Serum samples were obtained before and after sorafenib treatment from 115 consecutive patients [training set (n = 65) and validation set (n = 50)] with HCC and analyzed by multiple reaction monitoring-mass spectrometry (MRM-MS) to quantify candidate biomarkers.

Results: We verified a triple-marker panel to be predictive of the response to sorafenib by MRM-MS in HCC patients. This panel was a significant predictor (AUROC > 0.950) of the response to sorafenib treatment, having the best cutoff value by multivariate analysis. In the training set, patients who exceeded this threshold (0.4) had significantly better overall survival (median, 21.4 months) than those with lower values (median, 8.6 months; P = 0.001). Further, a value that was lower than this cutoff was an independent predictor of poor overall survival [hazard ratio (HR), 2.728; 95% confidence interval (CI), 1.312-5.672; P = 0.007] and remained an independent predictive factor of rapid progression (HR, 2.631; 95% CI, 1.448-4.780; P = 0.002). Consequently, when applied to the independent validation set, levels of the cut-off value for triple-marker panel maintained their prognostic value for poor clinical outcomes.

Conclusions: A discriminatory signature that comprises a triple-marker panel independently correlates with poorer survival and more rapid progression in HCC patients who are treated with sorafenib. These findings provide new insights into targeted proteomics-based biomarkers, which might engender individualized sorafenib therapy.

Keywords: Hepatocellular carcinoma, Targeted proteomics, Sorafenib, Biomarker

PE - 083

Impact of Pretreatment Contrast Enhancement Features on Radiotherapy Outcome in Hepatocellular Carcinoma

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Aims: In radiotherapy (RT) for hepatocellular carcinoma (HCC), little is known about pretreatment response prediction. Hypoxia of a tumor makes central necrosis, which is shown as consistent central enhancement defect (CED) in dynamic CT. We hypothesized that CED in pretreatment dynamic CT is a predictive factor of local failure after RT, in HCC. The purpose of this study was 1) to compare outcomes of RT in HCC with or without CED, and 2) to analyze blind reliability test for CED detection.
Methods: We retrospectively reviewed 392 patients who underwent RT for HCC at a single center, from January 2010 to October 2010. Among them, we excluded the patients who were not eligible for the present analysis as follows: 1) patients who had infiltrative HCCs with vascular invasion; 2) patients who received combined therapy with other treatment within 3 months; or 3) follow up (among survivors) periods were less than 2 years. Finally, a total of 202 patients were included. Tumor characteristics on pretreatment dynamic CT, RT dose, and outcomes were measured. With treatment outcomes blinded, presence of CED was decided by 5 physicians' agreements, and inter-observer reliability was tested. With tumor size and RT dose matched, 66 patients with or without CED were assessed by matched-pair analysis. Dose-response relationship was analyzed in both groups.
Results: Median follow up duration was 30.5 months (range 5.6 - 64.7), and median RT dose (equivalent 2 Gy dose (EQD2)) was 88 Gy (range, 31.3 - 125 Gy). CED was present in 20.8% of all patients. Local control rate (LCR) and overall survival (OS) were significantly worse in patients with CED (both $p < 0.001$). On multivariate analysis, local recurrence was correlated with tumor size, RT dose, and CED (odd ratios = 4.1, 10.2, 45.5, respectively). In matched-pair analysis, LCR was 26.4% and 79.2%, and OS was 39.4% and 66.7%, in patients with or without CED, respectively, at 2 years (both $p < 0.001$). Inter-observer reliability of CED detection was 89.5% ($p < 0.001$). Hypofractioned RT with EQD2 > 70 Gy showed significantly better LCR in both patients with and without CED ($p < 0.001$, $p = 0.039$, respectively).
Conclusions: In patients with HCC, a CED on pretreatment dynamic CT is a potent predictive factor for negative clinical outcomes, with good inter-observer reliability. To increase treatment outcomes in patients with HCC with CED, high-dose hypofractionated RT or other alternative treatment modalities should be considered.
Keywords: Hepatocellular carcinoma, Radiotherapy, Contrast enhancement, Clinical outcomes

PE - 084

Two Cases of Intraductal Papillary Neoplasm of the Bile Duct with Associated Invasive Carcinoma

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Aims: Intraductal papillary neoplasms of the bile duct (IPNB) have recently been proposed as one of the preinvasive lesions of cholangiocarcinoma. The reported malignant potential of IPNB ranges widely from 19.5 % to as high as 83 %. Due to the development to invasive cancer, IPNB is recommended to undergo definitive surgery. Herein, we report two cases of IPNB associated with invasive carcinoma.
Methods Presentation of cases:
A 74-year-old male patient admitted hospital because of cholangiocarcinoma occurred in IPNB. The tumor markers, (CEA; 3.96 ng/mL and CA 19-9; 28.3 U/mL), were within normal limits. Magnetic resonance cholangiopancreatography (MRCP) findings showed papillomatosis of the bile duct. Preoperatively, biopsy was performed by endoscopic retrograde cholangiopancreatography (ERCP), and then the pathology revealed adenocarcinoma. .
Second case was 61-year-old male patient. He knew liver cyst 4 years ago, and visited a hospital because the size of the cyst gradually increased. The tumor markers, (CEA; 0.67 ng/mL and CA 19-9; 7.77 U/mL), were within normal limits. In the computed tomography imaging, there were a cystic mass with mixed component in left hemiliver.
Results: In the first case, choledochoscopic finding during surgery showed IPNB up to right and left second order branch of the intrahepatic bile ducts, we perform a palliative Roux-en Y hepaticojejunostomy. In the second case, we performed laparoscopic left hemihepatectomy, and then the pathology revealed IPNB, high-grade dysplasia with multifocal associated invasive carcinoma.
Conclusions: IPNB is a rare benign tumor that possesses a high potential for malignant transformation. Although IPNB is a rare disease, it requires increased attention due to its high malignant potential.
Keywords: IPNB, Cholangiocarcinoma

PE - 085

A Randomized, Prospective, Comparative Study about Effects and Safety of Sorafenib vs. Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombosis

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Aims: The treatment responses of advanced hepatocellular carcinoma(HCC) with portal vein tumor thrombosis(PVTT) were not acceptable and treatment modalities were limited. So, we compared effects and safety of sorafenib vs. hepatic arterial infusion chemotherapy(HAIC).
Methods: We prospectively collected data of 58 advanced HCC with PVTT patients whose Child-Turcotte-Pugh(CTP) score range 5 to 7 in 6 university hospitals from January 2013 to Oct 2015. Each twenty nine patients were treated with sorafenib or HAIC.
Results: 1. The mean age was 60.2±8.4 years old and 89.7% of

the patients were male. Causes of HCC were HBV (67.3%), HCV (8.6%), alcohol (19.0%) and others (5.2%). CTP class A was 89.7%, modified Union for International Cancer Control (mUICC) stage IVa was 63.8%, tumor diameter >10cm was 55.2%, multiple tumor was 60.3%, infiltrative type was 56.9%, main PVTT was 63.8%, median AFP value was 240.4 ng/ml.
2. 29 patients were enrolled to each groups. Baseline characteristics(sex, mean age, cause of HCC, mUICC stage, size of tumor, number of tumor, type of tumor(nodular, massive, infiltrative, diffuse), location of PVTT(main, main+branch, branch). CTP class, median value of AFP) has no significant difference between two groups.
3. The objective response rate was 38.1% in HAIC and 4.5% in sorafenib group (p=0.003). In univariate analysis, treatment modality, main portal vein invasion, objective response, massive tumor type were significant prognostic factors of overall survival (p=0.012, 0.046, 0.011, 0.041) and treatment modality, tumor number, massive tumor type were significant prognostic factors of time to progress (p=0.004, 0.043, <0.01). In multivariate analysis, objective response was a significant prognostic factor of overall survival (p=0.048) and treatment modality was a significant prognostic factor of time to progress (p=0.016).
4. Major complications were neutropenia (6.9%, more than grade 3) and catheter-related complication (3.4%) in HAIC group, hand-foot syndrome (20.7%) and diarrhea (3.4%) in sorafenib group.
Conclusions: For treatment of advanced HCC with PVTT patient, HAIC can be a valuable treatment modality like as sorafenib and more large size of study is needed.
Keywords: Hepatocellular carcinoma, Portal vein tumor thrombosis, Sorafenib, Hepatic arterial infusion chemotherapy

PE - 086

Assocating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Huge Hepatocellular Carcinoma Combined with Liver Cirrhosis and Portal Hypertension

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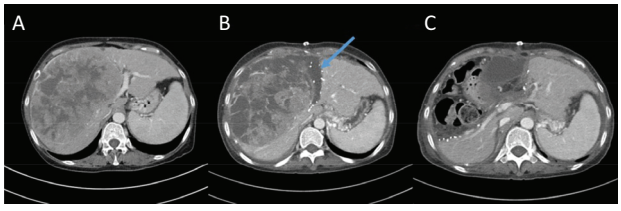
Introduction: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently been developed for patients with predicted insufficient future liver remnant volumes to induce more rapid hepatic hypertrophy and increase resectability. It has been usually performed for metastatic liver cancer from colorectal cancer, but few reports about ALPPS for hepatocellular carcinoma, especially in the liver cirrhosis combined portal hypertension were published. Especially, any treatment options of huge HCC under liver cirrhosis with portal hypertension were not proper. We reported a successful case of ALPPS for huge HCC combined with liver cirrhosis and portal hypertension.
Case report: A 58-year-old female patient was admitted for abdominal pain for 3 months. She had a history of chronic hepatitis B, but it was not treated. On abdominal CT, about 20 cm sized huge heterogeneously enhancing mass was identified and replaced to the right hepatic lobe. Right glisson and right hepatic vein were compressed and it invaded to middle hepatic vein and segment 4. Nodularity of liver surface, moderate splenomegaly and enlarged varices were identified. AFP level was severely increased to 158389 ng/mL and PIVKA-II level was over 100,000 mAU/mL. ICG 15(%) was checked to 48.2 %. It was suggested to severe liver cirrhosis and inoperable state. The future remnant liver volume(LLS+S1) on CT volumetry was 306 mL(291+15). Severe post-hepatectomy liver failure was strongly expected and so ALPPS was planned.
During 1st stage operation, the partition between left lateral section and S4, right anterior portal vein ligation was performed. The partition plane was covered with Proceed mesh. The reason of right anterior portal vein ligation was that centalhepatectomy was preferred to right tri-sectionectomy if right tri-sectionectomy would make post-hepatectomy liver failure even though ALPPS was performed. Total bilirubin level was increased to 2.22 mg/dL but CT volume of left lateral section was increased to 387 mL at postoperative 12 days. 2nd stage operation was performed at 14 postoperative days. During 2nd stage operation, anatomical central hepatectomy was performed without sacrifice of the right posterior section with right posterior glisson and right hepatic vein. Total bilirubin level was increased to 5.13 mg/dL on new postoperative 1 day, but it was recovered to normal range on postoperative 12 days. CT remnant liver volume(SLLS+S1+RPS) was 589mL(395+16+178) at postoperative 8 days although biloma was identified at resection area. She recovered at postoperative 1 month.
Conclusion: Although the validity and oncologic safety of ALPPS were not yet fully investigated, ALPPS for HCC under severe liver cirrhosis with portal hypertension was possible and more studies are needed to further evaluate its effectiveness and oncological outcomes.



PE - 087

Treatment Outcome and Prognosis of Patients with Hepatocellular Carcinoma with Inferior Vena Cava and/or Cardiac Invasion

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Aims: The incidence of hepatocellular carcinoma (HCC) extending to inferior vena cava (IVC) and/or right atrium (RA) is rare and median survival has been reported to be about 2 to 3 months. Although according to BCLC staging and treatment strategy, sorafenib or symptomatic treatment is recommended in these patients, some reports suggested that active treatment had resulted in prolonged survival. Thus, this study was aimed to investigate the efficacy of active treat-

ment for HCC patients with IVC and/or RA invasion and the causes of death.

Methods: A total of 2127 patients newly diagnosed as HCC from January 1, 2002 to December 31, 2014 at Seoul St. Mary's hospital were reviewed. Out of these patients, 44 had IVC and/or RA invasion at the time of diagnosis. Patients were divided into control group (n=10) in which only supportive care was given and actively treated group (n=34).

Results: In this study, median follow up period was 3.3 months. There was no significant difference between control and actively treated group in terms of age (57.4±14.3 vs. 52.4±12.4, p=0.28), CTP score (A/B/C, n=4/5/1, n=19/14/1, P=0.387) and number or the largest size of intrahepatic tumor. In treated group, transarterial chemoembolization (TACE, n=17, 49%) and hepatic arterial infusion chemotherapy (HAIC, n=15, 43%) were the most prevalent modalities and 4 patients additionally received radiation therapy. Median survival was 5.8 (range, 0.2-56.0) months for all patients. There was a significant difference in median survival between the control and treated group [median, 1.5 (range, 0.2.5-7.4) vs. 8.0 (range, 1.6-56.0) ; log-rank test, p=0.01]. Causes of death were investigated in 24 patients and these were tumor progression (n=13, 54.2%), liver failure (n=6, 25.0%), HCC rupture (n=3, 12.5%), infection (n=1, 4.2%) and ARDS (n=1, 4.2%).

Conclusions: Treatment group showed a better prognosis than control group. And half of patients died from cancer progression, not pulmonary embolism or heart failure by IVC and/or RA tumor thrombosis. Therefore active treatment could improve the survival rate in HCC patients with IVC and/or RA invasion. Further study with a larger population of subjects would be needed to verify these findings.

Keywords: HCC, Prognosis, IVC, Invasion

PE - 088

Sarcopenia May Be Associated with the Mortality in Patients with Hepatocellular Carcinoma

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Aims: Sarcopenia has known as an independent predictor of clinical outcomes in patients with hepatocellular carcinoma (HCC). In this study, we aimed to investigate the association of sarcopenia with the mortality in patients with HCC.

Methods: Total of 193 HCC patients were subjected. All enrolled patients had a computed tomography at the level of the third lumbar (L3) vertebrae to determine the L3 skeletal muscle index. Sarcopenia was defined using previously established cutpoints. They were followed up for a median 12 months (range, 1-80).

Results: Median age was 58 years (range, 36-86), 80% of patients were male, 62% Child -Pugh class A and 70% were positive for HBsAg. Only 23 patients (12%) could undergo curative treatment (surgical resection, liver transplantation, radiofrequency ablation) Sacopenia was present in 106 patients (55%). By univariate analysis, sarcopenia (OR=2.08; 95% CI 1.12-3.87: P =0.021), Child-Pugh score (OR=1.38; 95% CI 0.92-191.12: P <0.001), tumor number (OR=3.01; 95% CI 1.55-5.85: P=0.001), tumor size (OR=1.10; 95% CI 1.02-1.187: P =0.01), portal vein thrombosis (OR=3.00; 95% CI 1.45-6.21: P =0.003) and curative treatment of HCC (OR=0.13; 95% CI 0.04-0.39: P <0.001) were associated with mortality. By multivariate analysis, sarcopenia (OR=2.13; 95% CI 1.01-4.54: P =0.021) and curative treatment of HCC (OR=0.26; 95% CI 0.08-0.87: P=0.029) were closely associated with mortality. There was no correlation with age, gender, cirrhosis, diabetes mellitus, prevalence of hepatitis surface antigen positivity, underlying renal function, body mass index, platelet count, baseline AFP level, Child-Pugh score, tumor size, tumor number and portal vein thrombosis.

Conclusions: Our data suggested that sarcopenia and curative treatment of HCC may be closely associated with the mortality in HCC patients.

Keywords: Sarcopenia, Hepatocellular carcinoma, Mortality

PE - 089

Totally Intra-corporeal Laparoscopic Liver Resection for Rt. Posterior Segment by Extracorporeal Glissonian Approach with Hanging-over Maneuver

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Purpose: Glissonian approach is useful method in open hepatic resection. Glisonian approach have benefit of less blood loss, operation time saving and better oncologic outcomes. Totally intra-corporeal laparoscopic Rt. Posterior Sectionectomy is difficult to challenge and dangerous to surgeons on his initial stage for laparoscopic liver resection. Laparoscopic Glissonian approach with hanging-over maneuver is could be achived by isolation of Rt. Posterior Glissonian pedicle.

Method: The Glissonian approach with hanging-over method is well known method for open liver resection. And, it could be applied for laparoscopic liver resection for experienced HBP surgeons. The detailed knowledge of the segmental anatomy of the liver has led to a rapid evolution in resectional surgery based on the intrahepatic distribution of the portal triad.. This Glissonian sheath encloses the portal trinity. We describe the technique for laparoascopic approaching the Glissonian sheath and hence the hepatic pedicle structures and their branches by the intrahepatic posterior approch that allows early delineation of the liver segment without the need for ancillary techniques. Pedicle to Rt. Lobe and Lt. Lobe could be separated first. Then, pedicle to Rt. Anterior and Posterior segement could be isolated as whole Glissonian pedicle by laparoscopic approach.

Result: Especially rt. Posterior segment have large surface for surgical resection and difficulty for mobilization of Rt. Lobe. After passing the silicon tube through RPS Glissonian pedicle and with/without Rt. Hepatic vein, hanging over for Rt. Posterior parenchyma could be achived.

Conclusion: Moreover, laparoacopic Glissonian approach with modified hanging over maneuver could help the laparoscopic major liver section. Future prospectively, the usefulness of this technique for oncologic aspect and surgical result are also discussed.

PE - 090

Staged Partial Hepatectomy versus Transarterial Chemoembolization for the Treatment of Spontaneous Hepatocellular Carcinoma Rupture : A Multicenter Analysis in Korea

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Purpose: The long-term outcome in patients with spontaneous ruptured hepatocellular carcinoma (HCC) who received staged partial hepatectomy or transarterial chemoembolization (TACE) remains unclear. We compare the efficacy of staged partial hepatectomy or TACE for the treatment of spontaneous ruptured HCC.

Methods: This study is a retrospective analysis of a multicenter collected database of patients with newly diagnosed ruptured HCC. The survival curves for staged hepatectomy group and TACE-alone group were compared to evaluate the impact of treatment on patient prognosis. To identify prognostic factors for patient with spontaneous ruptured HCC, clinical characteristics at diagnosis of tumor rupture were investigated using univariate and multivariate Cox-regression analysis.

Results: Between January 2000 and December 2014, a total of 172 consecutive patients with newly diagnosed ruptured HCC were treated in six Korean centers. Among these 172 newly diagnosed ruptured HCC patients, 117 patients with Child-Pugh class A were identified: 112 patients initially treated with transcatheter arterial embolization (TAE) for hemostasis, 5 underwent emergency surgery for bleeder ligation. Among the 112 patients treated with TAE, 44 underwent staged partial heatectomy, 61 received TACE-alone, and 7 received conservative treatment after TAE. The staged partial hepatectomy group showed significantly higher overall survival than the TACE-alone group (P<0.001). Multivariate analysis showed that patients receiving TACE-alone, presence of portal vein thrombosis and pre-treatment transfusion above 1200 ml were associated with poor overall survival of patients with spontaneous ruptured HCC.

Conclusion: Our study indicates that staged partial hepatectomy may offer better long-term survival than TACE for resectable HCC with recent tumor rupture. And TACE remains a local therapy option for patients who do not eligible for surgery.

PE - 091

Prognostic Factors after Resection for Large Hepatocellular Carcinoma Over 5 cm

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Purpose: This study aimed to determine the factors that affect on the prognosis of hepatic resection for hepatocellular carcinoma (HCC) larger than 5cm, including the prognostic difference between tumor size 5-10cm and larger than 10cm.

Methods: The medical records of 114 patients who underwent hepatic resection for single HCC larger than 5cm were reviewed and analyzed retrospectively.

Results: In the analysis of the entire cohort of 114 patients, the 5-year overall and diseases-free survival rates were 50% and 29%, respectively. In comparison of survival rate between groups tumor size 5 to 10cm and larger than 10cm, the overall and disease-free survival rates were not significantly different, respectively (54% vs 41%, p=0.433 and 33% vs 23%, p=0.083). On multivariate analysis, positive hepatitis B, high PIVKA-II level over 200 mIU/mL, and vascular invasion (micro- and macrovascular invasion) were independent prognostic factors for recurrence after hepatic resection. However tumor size larger than 10cm was not significant for the recurrence after resection.

Conclusion: This study shows that surgical resection of solitary HCC larger than 5cm showed favorable overall survival. And there is no survival difference of tumors between 5-10cm and larger than 10cm.

PE - 092

Pathologic Response to Preoperative Transarterial Chemoembolization for Resectable Hepatocellular Carcinoma May Not Predict Recurrence after Liver Resection

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Purpose: Pathologic response (PR) predicts survival after preoperative chemotherapy and resection of a malignancy. Occasionally, transarterial chemoembolization (TACE) may be selected for preoperative management of resectable hepatocellular carcinoma (HCC). This study investigated whether PR to preoperative TACE can predict recurrence after resection for resectable HCC.

Methods: We conducted analysis of 106 HCC patients who underwent TACE followed by liver resection with a curative intent. The PR was evaluated as the mean percentage of non viable tumor area within each tumor. We divided the patients into three groups according to response rate: complete PR (CPR), major response (MJR: PR ≥50%) and minor response (MNR: PR <50%). The primary endpoint was disease-free survival, and the secondary endpoints were predicting factors for tumor recurrence and MJR+CPR.

Results: Among the 121 TACE patients, PR could be measured in 106 (87.6%). The mean interval between TACE and liver resection was 33.1 days. The 5-year disease-free survival rates by PR status were as follows: 40.6% CPR, 43.7% MJR, and 49.0% MNR (P=0.815).

There were also no significant differ-ences in overall survival between the three groups. Multivariate analyses revealed that microvascular invasion and capsular invasion (hazard ratio [HR]=11.224, P=0.002 and HR=2.220, P=0.043) were independent predictors of disease-free survival. Multivariate analysis of the predictors of above 50% PR revealed that only hepatitis B was an independent factor.

Conclusion: These data could reflect that the PR after TACE for resectable HCC may not be useful for predicting recurrence of HCC after resection.

PE - 093

Assocating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Huge Hepatocellular Carcinoma Combined with Liver Cirrhosis and Portal Hypertension

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Purpose: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently been developed for patients with predicted insufficient future liver remnant volumes to induce more rapid hepatic hypertrophy and increase resectability. It has been usually performed for metastatic liver cancer from colorectal cancer, but few reports about ALPPS for hepatocellular carcinoma, especially in the liver cirrhosis combined portal hypertension were published. Especially, any treatment options of huge HCC under liver cirrhosis with portal hypertension were not proper. We reported a successful case of ALPPS for huge HCC combined with liver cirrhosis and portal hypertension.

Methods: A 58-year-old female patient was admitted for abdominal pain for 3 months. She had a history of chronic hepatitis B, but it was not treated. On abdominal CT, about 20cm sized huge heterogeneously enhancing mass was identified and replaced to the right hepatic lobe. Right glisson and right hepatic vein were compressed and it invaded to middle hepatic vein and segment 4. Nodularity of liver surface, moderate splenomegaly and enlarged varices were identified. AFP level was severely increased to 158389 ng/mL and PIVKA-II level was over 100,000 mAU/mL. ICG 15(%) was checked to 48.2%. It was suggested to severe liver cirrhosis and inoperable state. The future remnant liver volume (LLS+S1) on CT volumetry was 306 mL (291+15). Severe post-hepatectomy liver failure was strongly expected and so ALPPS was planned.

Results: During 1st stage operation, the partition between left lateral section and S4, right anterior portal vein ligation was performed. The partition plane was covered with Proceed mesh. The reason of right anterior portal vein ligation was that cental hepatectomy was preferred to right tri-sectionectomy if right tri-sectionectomy would make post-hepatectomy liver failure even though ALPPS was performed. Total bilirubin level was increased to 2.22 mg/dL but CT volume of left lateral section was increased to 387 mL at postoperative 12 days. 2nd stage operation was performed at 14 postoperative days. During 2nd stage operation, anatomical central hepatectomy was performed without sacrifice of the right posterior section with right posterior glisson and right hepatic vein. Total bilirubin level was increased to 5.13 mg/dL on new postoperative 1 day, but it was recovered to normal range on postoperative 12 days. CT remnant liver volume (SLLS+S1+RPS) was 589mL (395+16+178) at postoperative 8 days although biloma was identified at resection area. She recovered at postoperative 1 month.

Conclusion: Although the validity and oncologic safety of ALPPS were not yet fully investigated, ALPPS for HCC under severe liver cirrhosis with portal hypertension was possible and more studies are needed to further evaluate its effectiveness and oncological outcomes.

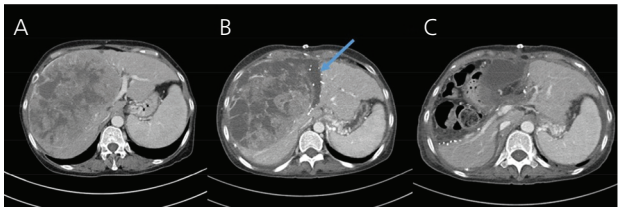

Figure 1. (A) preoperative CT shows that huge HCC (>20cm) compresses of right glisson; (B) CT between 1st stage and 2nd stage operation shows increased volume of left lateral section and the partition between left lateral section and S4 (blue arrow); (C) CT after 2nd stage operation shows successful central hepatectomy.

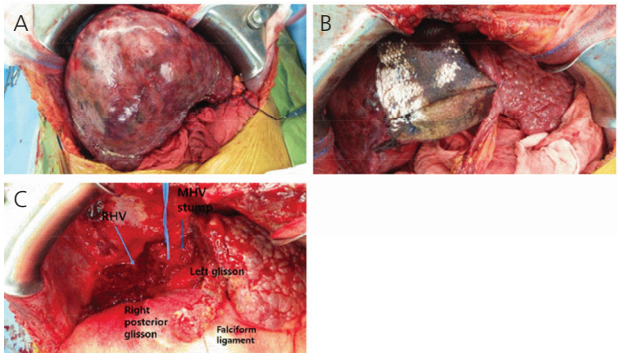

Figure 2. (A) Huge HCC underlying severe liver cirrhosis was identified during 1st operation, (B) 1st stage operation: the partition between left lateral section and S4, right anterior portal vein ligation The partition plane was covered with Proceed mesh, (C) 2nd stage operation: the anatomical central hepatectomy.

PE - 094

Totally Laparoscopic Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy Using Anterior Approach in HCC Patient with Type II Portal Vein Anomaly

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Purpose: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been gradually developed because of rapid

hypertrophy of the future liver remnant volume (FLR) despite of high morbidity. To minimize patient's postoperative pain and morbidity including wound complication by two consecutive major abdominal operations and bile leakage from liver cut surface due to severe adhesion after liver splitting of the first stage, we adopted totally laparoscopic approach and used composite mesh graft. Also, to maximize the oncologic efficacy, we adopted the "anterior approach" technique.

Methods: The patient was a 42 years old woman with huge hepatocellular carcinoma (HCC) in right lobe. She was hepatitis B carrier. Preoperative predicted FLR by CT scan was less than 30% and type II portal vein anomaly was also demonstrated. Totally laparoscopic approach was planned.

Results: In first stage, right anterior and posterior portal vein were dissected and tied. The "anterior approach" technique was applied for liver parenchymal dissection. The composite mesh graft was used to prevent severe adhesion on both liver partition surface.In second stage that performed on 9 days after the first operation, after the previously tagged two glissonian pedicles was transected, right inferior hepatic vein and hepatic vein sequentially transected. Transected right lobe was removed after complete mobilization. The patient discharged 7 days after 2nd operation and recovered without event.

Conclusion: Conclusively, totally laparoscopic ALPPS procedure is a feasible technique if we make throughout preparation for patient's safety and the onologic superiority, even in patient with complicated anatomic variation.

PE - 095

The Treatment Strategy of Hepatocellular Carcinoma Planned Hepatic Resection in Accordance with BCLC Staging Classification : Is It Golden Rule?

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Purpose: The Barcelona Clinic Liver Cancer (BCLC) staging classification comprises four stages that select the best candidates for the best therapies of hepatocellular carcinoma (HCC) currently available. Stage B and C patients may receive palliative treatments/new. End-stage disease (D) contain patients with extremely grim prognosis that should merely receive symptomatic treatment. But not a little studies for modification of this staging system have been set in motion accoding to new data from surgery. In this report, we retrospectively analyzed the result of surgical resection for the patient with HCC.

Methods: From March 2009 to June 2015, total 324 patient underwent liver resection in our center. We analyzed overall survival and disease free survival and their risk factor of this patient retrospectively. Their mean follow up period is 31months.

Results: The 3 year overall survival rate of BCLC B,C patient is 78.7%. The 3 year disease free survival rate on the same group, 48.4%. but the thing to notice is that even BCLC B-C group, in the cases with AFP $\leq$ 200 overall survival rate and disease free survival rate were significantly higher than those who did not. 3 year overall survival rate was 86.5% in the cases with AFP $\leq$ 200 and 58.6% in the cases with AFP>200 among the BCLC B or C patient (p=p.002). And 3 year disease free survival rate was 55.8% in the cases with AFP $\leq$ 200 and 28.0% in the cases with AFP>200 (p=0.005). According to the multivariative analysis of risk factor for disease recurrence, poor differentiation and BCLC B or C, AFP>200, the patient with esophageal varices were independent factor of recurrence.

Conclusion: In summury, by only BCLC staging system, surgical benefit can not given to sufficient patient with advanced HCC (BCLC B or C). Several significant factor had impact on disease recurrence such as tumor biology (AFP level) must be considered before surgery combined with BCLC staging system. And also BCLC must be moified as new data comes to light.

Liver Cirrhosis, Portal Hypertension with Cx. Basic

PE - 096

An Increased Incidence of Hepatocellular Carcinoma in Fibrotic Livers

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Aims: Liver fibrosis and its end-stage disease, cirrhosis, are major risk factors for hepatocellular carcinoma (HCC) and present in 80 to 90% of patients with HCC. Current genetically engineered mouse models for HCC, however, generally do not feature liver fibrosis, which is a critical discrepancy between human HCC and murine models thereof. In this study, we developed a transgenic mouse model of HCC with concurrent liver fibrosis induced by the treatment with carbon tetrarchloride.

Methods: Employing hydrodynamic transfection (HT), coupled with the Sleeping Beauty (SB) transposon system, liver was stably transfected with transposons expressing cMyc and a short hairpin RNA down-regulating p53 (shp53). A chronic liver injury model, induced by hepatotoxic carbon tetrachloride (CCl4), was applied to the transgenic mice, allowing cells expressing cMyc plus shp53 to become malignant in the background of liver fibrosis.

Results: Livers harvested about 3 months after HT had excessive collagen deposition and activated hepatic stellate cells surrounding the tumors. Hepatocarcinogenesis was significantly accelerated in the fibrotic livers compared to those of the control, significantly decreasing the life span of the mice. The tumor incidence and average number of tumors per mouse were significantly higher in the group treated with CCl4 compared to the vehicle-treated control mice, following HT ($p < 0.01$).

Conclusions: Transgenic model for HCC was successfully developed in fibrotic liver background. Liver fibrosis significantly accelerated tumor development in the liver.

Keywords: Liver fibrosis, Carbon tetrarchloride, HCC, Hydrodynamic transfection

PE - 097

Comparisons of Non Invasive Parameters on Fibrosis Regression in Chronic Hepatitis B Patients on Entecavir Therapy

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Background/aims: This study was conducted to compare non-invasive parameters on measuring liver stiffness in patients with chronic hepatitis B treated with Entecavir. Four non-invasive parameters: transient elastography (TE), aspartate platelet count ratio index (APRI), FIB-4 and fibrosis cirrhosis index (FCI) were used to measure liver fibrosis during treatment.

Methods: Chronic hepatitis B patients started on Entecavir as the first line therapy were recruited between November 2005 and July 2014. Among the population, patients who performed liver biopsy, transient elastography and laboratory tests to compute for APRI, FIB-4 and FCI were finally included.

Results: A total of 164 patients were included in the study. The median age was 48 years (112 were men at 68.3 %) and 92 patients (56.1%) were HBeAg-positive. 19 individuals were diabetic. A total of 121 (73.8%) patients had cirrhosis based on liver biopsy (using Metavir Score). During the follow-up (median 65.7 months), complete virology response (CVR) were achieved in 122 (74.4%) patients. The median value for liver stiffness by TE changed from 10.65 kPa (range 4 - 57 kPa) to 6.9 kPa (range 3.4 - 23.9 kPa); APRI from 0.61 (range 0.20 - 2.38) to 0.40 (range 0.13 - 1.14); FCI values from 2.26 (range -0.17 - 3.85 to 1.16 (range 0.15 - 4.93) and FIB-4 from 1.69 (range 0.18 - 7.72) to 1.68 (range 0.36 - 4.98). Hepatocellular carcinoma (HCC) developed in 23 (14 %) patients, 7.14% in group of fibrosis stage improved vs 21.3 % in groups of fibrosis stage not improved.

Conclusions: Long-term entecavir therapy improved liver stiffness profiles. Fibrosis indexes decreased from baseline median values were observed during the 5 year therapy with only TE and FCI showing improvement in fibrosis stage.

Keywords: Fibrosis, Cirrhosis, Non invasive parameters, Fibrosis regression

PE - 098

Effect of Rifaximin on the Hepatic Fibrosis in Bile Duct Ligated-rat Model

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Aims: Several recent studies suggest that the nonabsorbable antibiotic rifaximin could reduce endotoxemia and ameliorate hepatic fibrosis. The aim of this study was to investigate the effect of rifaximin on the hepatic fibrosis in animal model.

Methods: Adult Sprague-Dawley rats were allocated to 6 groups: sham-operated rats [G1 (n=6) and G4 (n=7)], rats underwent bile duct ligation (BDL) [G2 (n=4) and G5 (n=6)], and BDL rats treated with rifaximin (50 mg/kg/day by gavage feeding) [G3 (n=9) and G6 (n=5)]. G1, G2 and G3 were sacrificed on day 9. G4, G5 and G6 were sacrificed on day 21. Liver tissue was stored in -70°C refrigerator or fixed in formalin. Hepatic fibrosis was assessed by hydroxyproline assay and quantified by Sirius red staining with image analysis.

Results: The concentrations of hydroxyproline (μg/g liver tissue) were 236.4±103.1 in G1, 444.8±114.4 in G2, and 312.5±131.6 in G3. The concentration was higher in G2 than in G1 (p=0.025). However, there was no difference between G2 and G3. The degrees of collagen stain (%) were 0.22±0.04 in G1, 1.64±0.53 in G2, and 1.66±0.44 in G3. The degree was higher in G2 than in G1 (p=0.001). However, there was no difference between G2 and G3. The concentrations of hydroxyproline were 311.5±72.9 in G4, 1110.3±357.9 in G5, and 944.3±209.3 in G6. The concentration was higher in G5 than in G4 (p<0.001). However, there was no difference between G5 and G6. The degrees of collagen stain (%) were 0.19±0.03 in G4, 5.04±0.18 in G5, and 4.42±0.68 in G6. The degree was higher in G5 than in G4 (p<0.001). However, there was no difference between G5 and G6.

Conclusions: Rifaximin did not improve hepatic fibrosis in bile duct ligated-rat model.

Keywords: Hepatic fibrosis, Rifaximin, Bile duct ligation

PE - 099

Post-resection Prognosis of Combined Hepatocellular Carcinoma-Cholangiocarcinoma according to the 2010 WHO Classification

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Purpose: Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) is rare. We investigated the clinicopathological features of cHCC-CC and analyzed the prognostic influence of tumor type according to the 2010 WHO classification.

Methods: A cohort of 100 patients with cHCC-CC who underwent resection from July 2012 to June 2015 was selected as the study group. The control group comprised 200 propensity score-matched patients with intrahepatic cholangiocarcinoma (ICC).

Results: The mean tumor diameter of the cHCC-CC group was 4.4±2.8cm and 95 patients had single tumor disease. The cancers were classified as classical in 46 patients and subtypes with stem cell features in 54. The latter was further subdivided into typical (n=12), intermediate-cell (n=18), cholangiocellular (n=11), and un-

classified (n=13) subtypes. Their 1- and 3-year tumor recurrence vs patient survival rates were 31.7% vs 92.5% and 59.8% vs 77.3%, respectively (Fig. 1). There was definite prognostic stratification of tumor recurrence and patient survival rates according to the tumor type ($P \leq 0.008$). There was no difference in tumor recurrence compared with the ICC control group (P=0.523) but the cHCC-CC group showed better survival (P=0.008). The cHCC-CC group of subtypes with stem cell features showed better survival (P=0.001), but no significant survival difference was observed between the cHCC-CC classical group and the ICC control group (P=0.058).

Conclusion: cHCC-CC is a neoplasm with wide histologic diversity, indicating a strong association with hepatic progenitor cells. A close relationship exists between prognosis and tumor type according to the 2010 WHO classification. The complex mixture of histologic subtypes remains a challenge for the definitive classification of cHCC-CC.

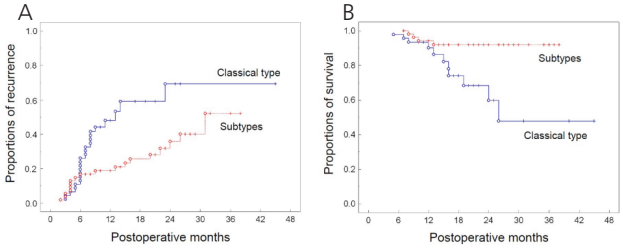

Figure 1. Tumor recurrence (A) and overall patient survival (B) curves according to the 2010 WHO Classification: classical type vs subtypes with stem cell features

Liver Cirrhosis, Portal Hypertension with Cx. Clinical

PE - 100

Pyelphlebitis Following Cyanoacrylate Injection into Duodenal Varix : A Rare Adverse Event

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We report a case of pyelphlebitis after duodenal varix obliteration using cyanoacrylate injection. A 55-year-old male presented with melena. Esophagogastroscopy revealed large duodenal varices with stigmata of recent bleeding and cyanoacrylate was injected. He was discharged from the hospital without further bleeding sign. Four months later, he developed fever and abdominal pain. Abdominal computed tomography and esophagogastroscopy showed disappearance of the duodenal varices but development of cholangitis and pyelphlebitis of the portal vein and superior mesenteric vein. The etiology of pyelphlebitis and treatment of duodenal varices are discussed.

Key words: Variceal bleeding, Duodenal varices, Cyanoacrylate injection, Pyelphlebitis

PE - 101

Diagnostic Accuracy of Magnetic Resonance Elastography with Liver Fibrosis Assessment in Chronic Viral Hepatitis Patients

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Aims: Magnetic resonance elastography (MRE) and transient elastography (TE) are emerging noninvasive methods as alternatives to liver biopsy. The diagnostic accuracy of TE was reported as reliable for cirrhosis, but controversial for significant fibrosis. The aim of this study was to determine the clinical performances of MRE for assessment of liver fibrosis in patients with chronic viral hepatitis.

Methods: One hundred and three patients with chronic viral hepatitis (HBV 78, HCV 25) underwent liver biopsy at CHA Bundang Medical Center in Korea between May 2012 and January 2015. We evaluated MRE and TE in comparison with the Metavir scoring system for assessing the severity of liver fibrosis. Liver stiffness measured by MRE showed reliable correlation with the liver fibrosis stage as confirmed by liver biopsy ($r=0.729$, $p<0.001$). The diagnostic accuracy was assessed by analysis of the area under the receiver operator characteristics curve (AUROC).

Results: The diagnostic performance of MRE was better (The AUROC of MRE, 0.88 for F1, 0.88 for F2, 0.89 for F3 and 0.93 for F4) than that of TE (The AUROC of MRE, 0.80 for F1, 0.83 for F2, 0.86 for F3 and 0.90 for F4). In contrast with TE, MRE could distinguish significant fibrosis from mild fibrosis. A cut-off value of > 4.23 kPa discriminates significant fibrosis from mild fibrosis with sensitivity of 80%, specificity of 81% ($p<0.001$).

Conclusions: MRE is a reliable noninvasive method for identifying significant fibrosis and cirrhosis in patient with chronic viral hepatitis. It has better diagnostic performance than TE for the diagnosis of significant fibrosis and cirrhosis.

Keywords: Liver fibrosis, Magnetic resonance elastography, Transient elastography, Diagnostic performance

PE - 102

Treatment of End-stage Liver Disease in the JSC National Scientific Center for Oncology and Transplantology, Astana, Kazakhstan: Views and Perspectives

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Aims: End-stage liver disease represents a major healthcare problem worldwide and in Kazakhstan, carrying a high risk for mortality. Around 1000 patients with end-stage liver disease need liver transplantation in Kazakhstan, more than 50 of them dying yearly without being transplanted. The aim of this paper was review treatment methods for end-stage liver cirrhosis in our center.
Methods: Results of various treatment options for end-stage liver disease patients, treated in JSC National Scientific Center for oncology and transplantology since June 2013 so far, were reviewed.
Results: Total of 18 liver transplantations, including 6 from cadaveric and 12 from live donors, were performed in our clinic since June 2013, so far. Etiology of liver disease was as follows: HCC (due to nonalcoholic steatohepatitis in 2, hepatitis B in 1) 3 patients, liver cirrhosis (due to alcoholic liver disease in 3, hepatitis C in 2, hepatitis B+D in 6, autoimmune hepatitis in 1, primary biliary cirrhosis in 2 and autoimmune hepatitis and hepatitis B in 1) 14 patients, remaining was 7-year old pediatric patient with biliary atresia. Out of 18 transplanted patients, 2 have succumbed in the early post-operative period due to hemorrhage, remaining 16 are followed-up, counting up to 32 months of disease and rejection-free survival.
Since the establishment of hepatology beds at department of general therapy in June 2015, total of 122 patients with liver cirrhosis and hepatocellular carcinoma were treated so far up to February 2016. Methods of treatment of hepatocellular carcinoma included transarterial chemoembolisation used 10 times in 6 patients, 1 patient has succumbed after 3 months of being diagnosed. Treatment options for portal hypertension in 113 liver cirrhosis patients included: esophageal varices ligation and sclerotherapy in 45 patients, splenic artery and esophageal varices embolisation in 22 patients with no complications dated and treatment with beta blockers in the rest of the patients. Out of 113 patients, 1 has succumbed due to the disease progression since start of follow-up in June 2015.
Conclusions: Liver transplantation is the only viable option for end-stage liver disease patients. Portal hypertension treatment options using endoscopic and endovascular methods may provide sufficient short-term effect with good safety profile while being waitlisted, thus making liver transplantation available for more patients.
Keywords: Liver cirrhosis, End-stage liver disease, Endoscopic variceal ligation, Splenic artery and esophageal varices embolisation

PE - 103

Risk Factors for Initial Treatment Failure and Short-term Mortality of Spontaneous Bacterial Peritonitis in Patients with Liver Cirrhosis

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Aims: We aimed to investigate the clinical factors associated with the treatment outcomes and short-term mortality of spontaneous bacterial peritonitis (SBP) in cirrhotic patients. We also evaluated the impact of hepatocellular carcinoma (HCC) on the treatment failure and mortality of SBP.
Methods: In this retrospective study, total 144 cases of SBP diagnosed between January 2004 and December 2014 were included. SBP was diagnosed based on a polymorphonuclear cell count in ascitic fluid of ≥250 cells/mm3 in the absence of data compatible with secondary peritonitis.
Results: The mean age was 58.2 years, 114 (79.2%) patients were men, and 53 (36.8%) patients were combined with HCC. Overall, the rate of initial treatment failure was 58/144 (40.3%). Patients combined with HCC showed higher rate of initial treatment failure compared to non-HCC patients (64.2% vs. 26.4%, P<0.001). In multivariate analysis, HCC (Odd ratio 7.71, P<0.0001), and serum creatinine level (Odd ratio 1.89, P=0.004) were independent factors for initial treatment failure. Furthermore, 7-day and 30-day mortality were 26/144 (18.1%) and 58/144 (40.3%) respectively. In addition, 30-day mortality was significantly higher in patients with HCC compared to non-HCC patients (64.2% vs. 26.4%, P<0.001). HCC (Odd ratio 5.11, P=0.009), serum creatinine level (Odd ratio 1.73, P<0.036), Child-Pugh score (Odd ratio 2.26, P=0.001) and treatment failure (Odd ratio 28.72, P=<0.001) were independent factors for 30-day mortality.
Conclusions: HCC and renal dysfunction was independent risk factors for initial treatment failure and poor short-term prognosis in patients with SBP.
Keywords: Spontaneous bacterial peritonitis, Hepatocellular carcinoma, Liver cirrhosis, Mortality

PE - 104

The Study for the Relation between Cardiac Diastolic Dysfunction and Prognosis in Patients with Decompensated Liver Cirrhosis

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Aims: Alteration of cardiovascular functions in patients with liver cirrhosis has been described and precedes hepatorenal syndrome and contributes to its development by aggravating the circulatory dysfunction. Left ventricular diastolic dysfunction (LVDD) constitutes the characteristics of cirrhotic cardiomyopathy. We evaluated the cardiac diastolic dysfunctions in liver cirrhosis with ascites or variceal bleeding and investigated the prognosis of decompensated liver cirrhosis.
Methods: We prospectively enrolled 83 patients with decompensated liver cirrhosis including ascites or variceal bleeding at the Daejeon St. Mary's hospital from April 2013 to April 2015. Cardiac function

of these patients was evaluated by a tissue Doppler imaging and conventional 2-D-echocardiography. LVDD was graded according to the American Society of Echocardiography guidelines. The primary endpoint was overall survival.

Results: LVDD was found in 60(71.4%) of the 84 patients. Its presence was not found to associate with the etiology and Child class. During follow-up, 18 patients had died; 17 had LVDD (17/60, 28.3%) and 1 (1/24, 4.1%) had not. Patients who died at the follow-up had a higher MELD score, hs-CRP, lower albumin and older age. Ratio of early diastolic annular velocity to peak early diastolic annular wave velocity (E/e') was the most significant marker for diastolic dysfunction. On Univariate analysis for overall survival, patients with LVDD (E/e'>9) had significantly poor prognosis compared with those without LVDD (E/e' <9) (14.9 vs. 26.6 months, respectively, P=0.021). Age, hs-CRP, child class were also related with survival outcome (P=0.025, 0.026 and 0.009, respectively). Multivariate analysis for survival, LVDD, Higher hs-CRP, Child class and MELD score also showed independent predictive factors of survival (P=<0.000, 0.021, 0.000 and 0.017, respectively)

Conclusions: LVDD is commonly associated with hepatic dysfunction in liver cirrhosis patients with decompensated complications while systolic function is maintained. Therefore, it may be important to monitor and closely follow up the patients with LVDD.

Keywords: Left ventricular diastolic dysfunction, Decompensated liver cirrhosis, Survival

PE - 105

The Safety and Efficacy of Plug-assisted Retrograde Transvenous Obliteration for the Treatment of Gastric Varices: Single Tertiary Hospital Experience

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Aims: Gastric variceal bleeding occurs less often than esophageal varices (EV), but bleeding from gastric varices (GV) has a poorer prognosis and is associated with more severe blood loss, a higher rebleeding rate, and a higher mortality rate. Although balloon-occluded retrograde transvenous obliteration (BRTO) has widely been performed for the control of GV, it have several limitations including complications. Vascular plug-assisted retrograde transvenous obliteration (PARTO) is recently introduced for the treatment of GV. Therefore, this study evaluated the clinical outcomes of PARTO for the treatment of GV bleeding.

Methods: From Oct 2012 to Jul 2015, 25 patients with GV who had undergone PARTO were retrospectively evaluated. Clinical and labratory data were analyzed to evaluate the clinical safety and efficacy of PARTO.

Results: Among 25 patients with GV, 20 patients had undergone PARTO for primary prophylaxis of GV hemorrhage and 5 patients had undergone PARTO for secondary prophylaxis of GV hemorrhage. The median age of patients was 68 (range, 44-85) and male predominant (15/25, 60%). 14 patients had Child-Pugh (CP) class A liver cirrhosis, 9 had CP class B, and 2 had CP class C at the time of PARTO. PARTO was technically successful in 23/25 patients (one: fail to lodge plug into gastrorenal shunt due to big gastrorenal shunt, one: fail to coagulation). Among 19 patients who underwent follow-up endoscopy or computed tomography (CT) of GV, 10 patients achieved eradication of GV and 8 patients exhibited marked shrinkage of the GV. During 9.76±9.93months (mean±SD) of follow-up period, rebleeding of GV was not occured. Procedure-related complications were occurred in 44% (11/25) and included fever (n=8) and abdominal pain (n=5). Worsening of EV occurred in three patients, and one of them had a active bleeding. Two patients exhibited aggravated ascites.

Conclusions: PARTO is a technically successful and clinically safe and effective procedure for the treatment of GV.

Keywords: Gastric varix, Variceal bleeding, PARTO

PE - 106

Presence of Anemia Predicts Advanced Grade at Presentation in Patients with Hepatic Encephalopathy

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Aims: The objective of our study was to assess the impact of anemia on HE grade at presentation.

Methods: Consecutive patients of HE admitted in the medical wards of Mayo Hospital, Lahore during March 2010 and May 2010 were enrolled in the study. HE grade at presentation was assessed by using West-Haven Criteria. Complete blood count, bleeding profile, liver function tests and ultrasound was done in emergency at presentation. Anemia was defined as hemoglobin level less than 12 g/dl. Univariate and multivariate logistic regression analysis was done to assess the impact of anemia on hepatic encephalopathy grade at presentation. P value <0.05 was considered significant.

Results: 61 patients were included in the study. 20% patients were in grade 1 HE; 20% in grade 2; 39% in grade 3; and 21% in grade 4 HE. Advanced grade HE was defined as HE grade >2. On univariate analysis prothrombin time >15 seconds, diabetes, esophageal varices on endoscopy, and anemia were significant predictors of advanced grade HE (p values: 0.048, 0.048, 0.039, 0.037). Hypoalbuminemia was less common in advanced grade HE patients (p, 0.004). Child Pugh Score and MELD Score had no relation with HE grade at presentation. All the significant factors in univariate analysis were included in the multivariate logistic regression model. Only anemia was significant predictor of advanced grade HE in multivariate analysis (p, 0.018).

Conclusions: Sixty percent of HE patients present with advanced grade. Anemia is associated with advanced HE grade at presentation.

Keywords: Anemia, Cirrhosis, Hepatic encephalopathy, Risk factors

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Hyponatremia in Decompensated Cirrhosis: Is It Associated with More Severe Disease?

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Aims: The aim of our study was to evaluate whether there is any association between hyponatremia and severity of decompensated cirrhosis.

Methods: Consecutive patients of decompensated cirrhosis presenting at three tertiary care hospitals were included in the study. Hyponatremia was defined as serum sodium levels of <135 mEq/L. Patients with Child-Pugh Class A and B were considered having mild disease and Class C patients were categorized as having severe disease.

Results: A total of 202 patients were included in the study with male preponderance (53%). Patients presenting with Child-Pugh Class A, B and C were 16 (6.9%), 74 (36.6%) and 114 (56.4%) respectively. Hyponatremia was present in 37.3% of the patients. On bivariate analysis, factors associated with severe decompensated cirrhosis (Child-Pugh Class C) were total protein <6 g/dL (p, 0.002), hemoglobin level <12 g/dL (p, 0.006), APTT >35 seconds (p <0.001), AST >35 IU (p, 0.03) and serum sodium level <135 mEq/L. Thrombocytopenia, raised blood urea, raised serum creatinine, and hyperkalemia were not associated with severity of decompensated cirrhosis as was the etiology of cirrhosis (Hepatitis C versus non-hepatisis C). Variables significant in the bivariate analysis were then included in the multivariate logistic regression model. All the variables remained significant except anemia which did not show any association with severity of disease in multivariate analysis.

Conclusions: One third of the patients with decompensated cirrhosis in the present study had hyponatremia which was associated with less severe disease (lower Child-Pugh Class) at presentation.

Keywords: Hyponatremia, Cirrhosis

Liver Failure, Acute

PE - 108

A Case of Hepatogastric Fistula as a Rare Complication of Pyogenic Liver Abscess

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Aims: A cases of hepatogastric fistula secondary to a liver abscess is a rare complication. We present a case of pyogenic liver abscess which was complicated with the development of a hepatogastric fistula and it was managed with surgical excision.

Methods Results: A 88-year-old woman presented with generalized weakness and fever for 3 days. The laboratory tests revealed a white blood cell (WBC) count of 11,380/μL and C-reactive protein level of 24.37mg/dL. A computed tomography (CT) scan of the abdomen showed 5cm sized lobulated hypodense lesion with internal septa and marginal enhancement in the left lateral segment of the liver. The appearance was suspicious of an early liver abscess but coexistence of cholangiocarcinoma cannot be ruled out.

An ultrasonography-guided aspiration and biopsy was performed after 9 days of hospitalization. the microscopic examination showed no malignant cells and the pus culture revealed Klebsiella pneumonia. Gadoxetate-disodium-enhanced magnetic resonance imaging was performed for follow up. The anterior wall of the stomach was found in close proximity to the liver abscess but the communication between gastric lumen and liver was not evident. The mature appearance compared to initial CT scan, ultrasonography-guided percutaneous drainage of liver abscess was performed. contrast media injected through the drain appeared fistulous tract between liver and stomach. Resection of involved portion of the stomach and the liver was done and 2 weeks after surgery patients was discharged.

Conclusions: In our case, drainage procedure was deferred due to initial immature feature of abscess cavity, but it resulted in spontaneous fistulization into the stomach. This implies that proper drainage of pyogenic liver abscess is advised to prevent a spontaneous abscess rupture or fistularization into the adjacent structures.

Keywords: Hepatogastric fistula, Pyogenic liver abscess

PE - 109

Investigation of Hepatocyte Induced by Direct Reprogramming as Novel Therapeutic Tool for Liver Regeneration and Cirrhosis

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Aims: Liver disease is the fifth biggest killer in Korea. Currently, two major treatments of severe liver disease, liver transplant (LT) and anti-tumor agent, are limited due to availability of donor and side-effects. Therefore, liver regeneration is an important component of the reparative process following liver injury and surgical resection. In this study, we investigated the possibility of using induced hepatocyte (iHep) that were generated by direct reprogramming from fibroblast to promote liver regeneration in mouse model of acute liver failure.

Methods: Acute liver failure model was generated in 8weeks of BALB/C nude mouse by intraperitoneal injection of CCl4 (tetra-chloride, 0.5μl/g mix with Corn oil 1:3). After 24hr CCl4 injection, GFP-iHep(GI) and GFP-MEF(GM) were administered by intrasplenic injection. Serum and livers were collected at specified time points (0, 4, 24, 48, 72hr post cell injection). Serum ALT and AST were measured by ELISA. Degree of liver injury is confirmed by Hematoxylin-Eosin (H&E) staining. Immnunofluorescence (IF) staining

was performed on slices of formalin tissues. Tissue proteins were extracted by Tissue homogenizer and used for Western Blot analysis. **Results:** Hematoxylin-Eosin (H&E) staining confirmed CCl4-induced acute liver injury. Consistent with previous reports, serum ALT/AST levels were peaked at 24hr after CCl4 injection. Besides, iHep injection significantly lowered serum ALT/AST levels than MEF injection did. Through IF staining, we found that intrinsic GFP fluorescence and alpha-GFP were co-localized nearby damaged portal vein area, indicating that the injected iHep has been successfully migrated to the damaged area of liver. Moreover, Albumin also co-localized with intrinsic GFP fluorescence. Also, western blot showed that iHep were stay still in liver upto 72hours post cell injection. These results indicate that iHep was migrated to liver and functioned as primary hepatocyte. **Conclusions:** We confirmed that liver injury were occurred by CCl4 and cells were migrated to liver through intrasplenic injection and keep condition in a few days. Moreover, Cells were function as primary Hepatocyte by co-staining with liver function marker such as Albumin. These result suggested that iHep may support liver repair, promote liver regeneration, fibrosis resolution or new blood vessel formation. **Keywords:** Stem cell, Direct reprogramming, Liver regeneration, Liver cirrhosis, Acute liver injury

PE - 110

Dynamic Risk Prediction of Hepatocellular Carcinoma Development Using Risk Prediction Models in Patients with Chronic Hepatitis B

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Aims: Recently, several risk prediction models for hepatocellular carcinoma (HCC) development have been proposed for patients with chronic hepatitis B (CHB). However, the clinical implication of the changing values in risk prediction models during follow-up is not known. Thus, we investigated whether the dynamic changes in risk prediction models measured at different time points can assess the changing risk of HCC development.

Methods: A total of 1,397 patients who underwent baseline liver stiffness (LS) measurement using transient elastography (TE) between 2006 and 2014 were recruited for retrospective analysis. All patients received 2nd LS measurement with more than 6 months of time interval. The accuracy of risk prediction models for HCC including CU-HCC, REACH-B, LSM-HCC, and modified REACH-B (mREACH-B) were calculated.

Results: The median age of the study population (931 men and 466 women) was 48.2 years at 1st LS measurement and 50.0 years at 2nd LS examinations, respectively. The median LS value, CU-HCC, GAG-HCC, REACH-B, LSM-HCC, and mREACH-B at 1st LS measurement were 11.8 kPa, 10.0, 85.4, 9.2, 11.5, and 8.3, respectively. On-going antiviral therapy at 1st LS measurement was identified in 475 (34.0%) patients. During the follow-up period (median 68.0 months), 87 (6.1%) patients developed HCC. Patients with HCC had significantly higher age, the proportion of diabetes and hypertension, prothrombin time, LS value, and values of all risk prediction models (all $p<0.05$), whereas they had significantly lower serum albumin level and platelet count (all $p<0.05$). On multivariate analysis at 1st LS measurement, all risk prediction models were independent predictors of HCC development [hazard ratio (HR) 1.049-1.355, all $p<0.05$] along with age, male gender, and diabetes, hypertension, prothrombin time, and serum albumin (all $p<0.05$). Similarly, risk prediction models were independent predictors of HCC development (HR 1.082-1.174, all $p<0.05$), along with age, male gender, diabetes, serum albumin, platelet count, and alpha-fetoprotein (all $p<0.05$), in multivariate analysis at 2nd LS measurement. However, the changes or % chance of risk prediction models between 1st and 2nd LS measurement were not significant in predicting HCC risk (all $p>0.05$). Among risk prediction models, mREACH-B at 1st LS measurement showed the significantly highest area under receiver operating characteristic curve (AUC) to predict HCC development at 7-years than other models including CU-HCC, REACH-B, and LSM-HCC (0.805 vs. 0.681-0.776 in a subgroup with antiviral therapy and 0.790 vs. 0.681-0.730 in a subgroup without antiviral therapy). In addition, mREACH-B at 2nd LS measurement showed the significantly highest (AUC) at 7-years than other models (0.791 vs. 0.714-0.760 in a subgroup with antiviral therapy and 0.798 vs. 0.714-0.760 in a subgroup without antiviral therapy).

Conclusions: Risk prediction of HCC development was feasible using the value of risk prediction models at different time points in patients with CHB, not the change or % changes in their values between two time-points. Because mREACH-B performed best in predicting HCC development among several risk prediction models, its incorporation into surveillance strategy should be tested in the future. **Keywords:** HCC, Chronic hepatitis B, Risk prediction model, Dynamic

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MELD Score and Liver Stiffness Are Predictive for the Development of Acute Decompensation that Induce Acute-on Chronic Liver Failure

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Aims: The risk estimation for the future development of AD that causes ACLF (AD-ACLF) is essential for the management strategies of cirrhotic patients. In recent reports, non-hemorrhagic AD is increasing and has more roles in the development of ACLF. The aim of this study is evaluation about the prognostic factors in the prediction of future AD-ACLF development.

Methods: For 25.1 months of median follow up, 379 cirrhotic patients(male 317, 83.6%/alcohol related patients 295(77.8%)) who performed baseline hepatic venous pressure gradient(HVPG), serologic tests and liver stiffness(LS) measurement using transient elastography(Fibroscan) have been prospectively followed for the development events including AD-ACLF. The first episode of AD-ACLF was

decided as an event. Through binary logistic regression analysis, parameters that showed P < 0.1 were selected and Cox proportional hazard model was performed.

Results: 63 patients developed AD-ACLF (16.6%) during the follow up period. Among AD-ACLF, non-hemorrhagic events (ascites, encephalopathy, infection includes SBP, jaundice) were more common (39 patients) than hemorrhagic events (GI bleeding) (24 patients). In the univariate analysis, Child-Pugh score (CP score), MELD score, HVPG, LS showed significant relation with the development of AD-ACLF. In Cox proportional hazard model analysis (adjusted by age, sex, alcohol drinking state) for the AD-ACLF development using CP, MELD score and HVPG, only MELD score showed significant hazard ratio (HR) 1.100 (1.010 - 1.197, P = 0.028). HVPG showed borderline value (HR 1.048, 0.999-1.099, P = 0.56) and CP score was not significant (HR 1.154, 0.975-1.367, P = 0.95). When LS was added in this model, MELD (HR 1.122, 1.027-1.225, P = 0.01) and LS (HR 1.023, 1.008 - 1.038, P = 0.003) showed significant predictive value but HVPG and CP score did not. Especially, for the non-hemorrhagic events, MELD (HR 1.215, 1.063-1.358, P = 0.001) and LS (HR 1.034, 1.014 - 1.054, P = 0.001) showed significant predictive value. In contrast HVPG and CP score was not significant (P = 0.447 and 0.499 respectively).

Conclusions: High MELD and LS were significant risk factors for the development of ACLF inducing AD. Moreover contrary to HVPG, MELD and LS showed high risk in the development of non-hemorrhagic AD. These findings are relevant to recent increase of clinical significance of non-hemorrhagic AD in ACLF and cirrhosis.

Keywords: MELD score, Liver stiffness, Acute decompensation, Acute-on Chronic liver failure

PE - 112

Features of Care the Pregnant Woman after Liver Transplantation

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Aims: As known the first case of pregnancy after liver transplantation has been in 1978 (Armenti VT1 et. al., Liver Transpl. 2000).

During three years 127 living donor liver transplantations has carried out in Kazakhstan and our report represents the first successful pregnancy and childbirth after liver transplantation.

Methods: Our patient is 27 years old for long period suffered from liver cirrhosis caused by autoimmune hepatitis. In December 2013 orthotopic transplantation of right liver lobe from a living related donor was performed. The donor was her elder brother.

Results: In postoperative period it was portal vein thrombosis which treated by heparin monotherapy. No other complications found in late period after transplantation. The standard third-component immunosuppressive therapy (CI + MMF + GCS) was applied during the first year after transplantation. One year later it was suddenly known that patient is pregnant and it was 2 week of pregnancy when MMF application was canceled. First signs of liver rejection was appeared on 18-20 weeks where sensitization of HLA class 1 was 0% and HLA class 2 consisted 91%. As a main therapy pulse therapy with GCS and plasmapheresis were performed.

During observation all signs of rejection and laboratory data decreased in 4 weeks and patientperformed a screening of fetus where no pathological alterations were found.

On 40 weeks delivery was successfully done by Cesarean section. The child was male with weight - 2830 g, and height - 54.3 cm and without no visible any defects.

Conclusions: In our case, it was an acceptable outcome for both mother and baby, although considered a high risk pregnancy. Regarding our data there is no evidence of specific structural malformations among children born to female liver transplant recipients, but it is still under observation when it should be decided with immunosuppressive therapy alterations.

Keywords: Liver, Transplantation, Pregnant, Acute

PE - 113

A Case of Acute Fatty Liver of Pregnancy Combined with Acute A Viral Hepatitis

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Acute fatty liver of pregnancy, characterized by microvesicular fatty infiltration of hepatocytes, is a disorder which is unique to human pregnancy. It was described in 1940 and was initially thought to be universally fatal. However, early diagnosis and prompt delivery have dramatically improved the prognosis, and maternal mortality should now be the exception rather than the rule. Acute fatty liver occurs typically in the third trimester. The disease is always present before delivery, although it is not always diagnosed prior to delivery. A 34-year-old female at 36-week gestation, presented with generalized myalgia, cold sweating, headache, easy fatigue, dark yellowish urine. She didn't have any specific past history. Physical examination revealed icteric skin color and dark yellowish urine. Her temperature was 37.9℃, pulse rate was 98/min, respiratory rate 20/min, and blood pressure 90/60mmHg. Ultrasonography reveal IUP around 36 weeks, low parenchymal echoes with GB wall edema and sludges from suspicious acute hepatitis and fatty changes of liver.

Initial laboratory finding revealed no anemia, no thrombocytopenia and PT 25.9sec prolongation, INR 2.33, aPTT 36.9sec, fibrinogen 2.38g/L, antithrombin III 53%, D-dimer 26.38ug/ml, FDP 95.2ug/ml, AST > 10,000 IU/L, ALT 2,100 IU/L, protein 5.62g/dl, albumin 3.12g/dl, total bilirubin 3.06mg/dl, direct bilirubin 1.86mg/dl, r-GT 73IU/L. Influenza test was negative. Blood culture was no growth. Serology tests like CMV, EBV, HBsAg, HCV, HEV and HIV were all negative except anti-HAV IgM positive. A presumptive diagnosis of AFLP and acute A viral hepatitis was made.

It was decided to perform an emergency lower segment caesarean section was performed 23 hours after admission. After delivery, laboratory finding was dramatically improved except bilirubin, that is, AST 4,520 IU/L, ALT 1,180 IU/L, protein 6.16g/dl, albumin 3.53g/dl,

and total bilirubin 3.88mg/dl, Anti-HAV IgM was still positive. Twenty days later, laboratory finding revealed AST 69 IU/L, ALT 12 IU/L, total bilirubin 14.74mg/dl. Although bilirubinemia was continued, the increment stopped. So we planned discharge. She was discharged on hospital day 21. Seven days later, on outpatient department total bilirubin fell to 8.84mg/dl.

This report is concerned with a case of 34-year-old female at 36-week gestation with AFLP and acute A viral hepatitis. We believe that this is the first case report of AFLP with acute A viral hepatitis in the world.

Keywords: AFLP, Acute A viral hepatitis, Acute liver failure

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A Case of HELLP Combined with AFLP

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HELLP is an acronym that refers to a syndrome characterized by hemolysis with a microangiopathic blood smear, elevated liver enzyme, and a low platelet count. It probably represents a severe form of preeclampsia, but the relationship between the two disorders remains controversial.

HELLP may be difficult to distinguish clinically from AFLP since both occur at the same time in gestation and share several clinical features. A 37-year-old female at 25-week gestation, twin pregnancy, presented with labor pain, abdominal pain, spotting vaginal bleeding. She didn't have any specific medical history. Physical examination revealed alert mental status, acute ill looking appearance. Her blood pressure 124/67mm Hg. Initial laboratory finding revealed mild anemia, no thrombocytopenia, PT 11.0 sec, INR 1.00, aPTT 25.6 sec, AST 34 IU/L, ALT 37 IU/L, protein 6.36g/dl, albumin 3.28g/dl, total bilirubin 0.28mg/dl and no proteinuria. Serology tests like HBsAg, HCV, HIV and HAV were all negative. We tried to suppress premature labor using tocolytics.

After fourteen days, liver function test abruptly increased from 71 to 1,680 and from 53 to 840, respectively AST and ALT during 2 days. In the same period, platelet fell from 183,000/uL to 23,000/uL. LDH was 2,192 IU/L. PT was still normal. Ultrasonography revealed IUP around 27 weeks, hepatomegaly with increased periportal echogenicity and secondary GB wall mild swelling, that is, hepatitis finding and increased parenchyme echogenicity of liver, that is, underlying severe fatty liver. Although we did not check hemolysis in PB smear, presumptive diagnosis of HELLP was made.

It was decided to perform an emergency lower segment caesarean section performed after about 5 hours. One day later, laboratory finding was aggravated, that is, AST 4,900 IU/L, ALT 1,790 IU/L, protein 4.24g/dl, albumin 2.48g/dl, PT 17.3 sec, INR 1.57, aPTT 33.6 sec, fibrinogen 1.71 g/L, antithrombin 60%, platelet 29,000/uL. Bilirubin increased from 1.19mg/dl to 3.34mg/dl next five days. It revealed AFLP feature. We did supportive care. After six days later, overall finding was improved. There was no hemolysis in PB smear.

This report is concerned with a case of 37-year-old female at 25-week gestation with HELLP and AFLP. We guess that this case is the mixed type with HELLP and AFLP.

Keywords: HELLP, AFLP, Acute liver failure

PE - 115

Prevalence and Predictors of Thrombocytopenia in Advanced Liver Disease

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Aims: To study clinical, laboratory and demographic predictors of thrombocytopenia in advanced liver disease.

Methods: 248 patients with decompensated cirrhosis (DC) (age range: 30-75 years; majority with chronic C hepatitis (78 %)) were prospectively analyzed. The platelet count with cut-off value of \150,000/lL was taken as thrombocytopenia. Patients with and without thrombocytopenia were correlated with patients' characteristics, such as demographics, prevalent extra hepatic diseases, therapeutic interventions (endoscopy, band ligation and interferon therapy), clinical signs and laboratory variables.

Results: 248 patients showed following distribution according to CP classification: A; 7 %; B; 30 % and C; 63 %. Hepatitis C (83 %, P = 0.009) demonstrated strong correlation but hepatitis B infection and alcohol failed to show any significant association with thrombocytopenia (P[0.05). People with splenomegaly (73 %, p = 0.000) and elevated ALT levels ([35 IU) were more prevalent in thrombocytopenia group (96 %, P = 0.019). Deranged clotting parameters PT ([15 sec, 96 %, p = 0.001) and aPTT ([35 s, 86 %, p = 0.023) were strongly associated with thrombocytopenia. However no statistically significant association was observed between demographic variables, MELD score, CP classification, extra-hepatic diseases, therapeutic interventions and other clinical signs and laboratory tests (p[0.05 for all).

Conclusions: Hepatitis C infection is an independent predictor of thrombocytopenia in DC. Combination of splenomegaly, elevated ALT, deranged clotting parameters can predict thrombocytopenia in advanced liver disease.

Keywords: Thrombocytopenia, Cirrhosis

Liver Transplantation

PE - 116

Acute Graft versus Host Disease Following Deceased Donor Liver Transplantation: A Case Report

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Aims: To report our experience of gaft vesus host disease(GHVD) after liver transplantation.

Methods Results: A 49 year old male hepatitis B virus carrier was diagnosed with hepatocellular carcinoma which had treated by TACE previously.
Preoperative cytomegalovirus (CMV), Epstein Barr virus, herpes simplex virus and autoimmune antibody series were negative. He received a liver transplant from a 15-year-old cadaveric male donor.
He was discharged at day 17 following the transplantation without any other complications.
On post-operative day (POD) 24, the patient was readmitted with a fever of unknown cause, a scattered skin rash and diarrhea. After admission, his blood cell count revealed pancytopenia.
A diagnosis of GVHD was confirmed following a skin biopsy which showed interface lymphocytic infiltrate that are largely centered on the dermal-epidermal junction.
On POD 30, the patient was treated with steroid pulse therapy (1g bolus for 1-3days and taper to 1-2mg/kg) as maintenance immunosuppression (tacrolimus, mycophenolate mofetil) and etanercept 25 mg twice a week.
Despite of antiviral and antifungal agent treatment, the patient was died to infections including CMV and aspergillus, and multiple organ failure at POD 46.
Conclusions: An effective therapeutic strategy for the treatment of GVHD following liver transplantation is not yet established, and further research is required to such a regimen being developed.
Keywords: GVHD, Liver transplantation, Steroid pulse therapy, Etanercept

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Transplant Program Development in Kazakhstan: Experience of 6 Years

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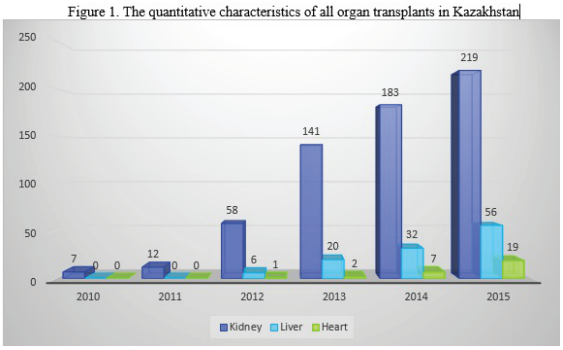
Aims: The aim of this analysis was to present the overall results of transplant service development in Kazakhstan.
Background: Kazakhstan as the one of the fast developing countries in Central Asia has been improving the development of organ transplantation since 2010. There are 9 national and city level hospitals performing kidney, liver and heart transplantations in two major cities Almaty and Astana. A coordination center for organ transplantation was established in 2013 with the purpose of developing cadaveric donation service in Kazakhstan. In all 16 regions of our country we have transplant coordinators who work on finding potential donors, talking to their relatives, and making organ preservation. Considering the huge territory of the country there is a sanitary aviation service specially prepared for organ transportation, the special team for organ harvesting and for recipients.
Methods: Prospective study started from 2010 at our center included all performed liver transplants and other organ transplants to analyze and follow up their results. Numbers are shown in percentages in Figure 1. The quantitative characteristics of all organ transplants in

Figure 1. The quantitative characteristics of all organ transplants in Kazakhstan



Kazakhstan.
Results: Overall, 760 patients had undergone transplantations of kidneys, liver and heart for the last 5 years. The first kidney transplantation from a cadaveric donor performed in 1979, and this date considered as a beginning of the organ transplantation development in the Republic of Kazakhstan (RK). For the first time in our country, the multi-organ harvesting of organs: kidneys and the heart from cadaveric donor was performed in 2012. Our national center became a pioneer in performing liver transplantation from a cadaveric donor since 2013. The same year, the first pediatric liver transplantation from a living donor was carried out for a 6-year-old child. Starting from 2013 in collaboration with transplant surgeons from Turkey and South Korea many hospitals started to develop living donor liver transplant programs. Figure 1 illustrates the quantitative characteristics of organ transplants carried out in the Republic of Kazakhstan for the period from 2010 (including) to 2015.
Conclusion: Our experience of Transplant program development highlights the demands of our population in organ donors with high mortality on a waiting list (72%). Thus, the development of living donor transplantation and overall transplant service will increase survival and quality of life of patients with end stage diseases.
Keywords: Liver transplantation, Transplant development

PE - 118

Pediatric Liver Transplantation Experience in Kazakhstan

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Aims: The aim is to analyze the first results of pediatric liver transplantation experience.
Currently in Kazakhstan on the waiting list for liver transplantation there are approximately 22 children various congenital or acquired liver pathologies. Most of the children with end stage liver disease need a donor organ transplant before the age of 1 year old. During the period from 2012 to 2015 at National Research Center for Maternity and Child in Astana, there are total of 6 pediatric living donor liver transplantations were performed in Kazakhstan. In all cases, the left lateral segment of the donor liver was allocated for transplantation. Age of recipients ranged from 5 months up to 6 year old. The donors are close relatives of the recipient, their age ranged from 24 to 36 years. In 5 out of 6 cases in children under

the age of 1 year old the etiology of liver cirrhosis was biliary atresia. In a 6 y.o. child the underlying cause of cirrhosis was autoimmune hepatitis. All liver transplantation performed with the participation of foreign experts from India, Turkey, and The Republic of Belarus.
Methods: Prospective study from the start of the first pediatric liver transplantation.
Results: Postoperative complications were not observed in donors. One child under the age of 5 months had a PO-complication as hepatic artery thrombosis (HAT). The surgical actions to fix the vascular damage were unsuccessful and the child was taken by sanitary aviation to hospital in Istanbul, Turkey, where he had another liver transplantation from a living donor. In the remaining five recipients there were no complications observed, and they discharged from the hospital.
Due to the severe shortage of donors, the mortality rate of children on a waiting list is up to 54%.
Conclusions: The lack of experience of local transplant surgeons in carrying out highly advanced surgeries in young children, forcing patients to carry out similar operations in foreign clinics by governmental funding or on their own expense. The most common surgery for liver transplantation Kazakhstani children held in South Korean hospitals, Germany, Turkey, India. On behalf of our colleagues and patients we want to thank our friends - colleagues from South Korea, Turkey, India, for their help and support in the development of transplantation in the Republic of Kazakhstan.
Keywords: Pediatric liver transplantation, Liver transplantation, End stage liver diseases, Biliary atresia

PE - 119

The First Successful Case of Living Donor Liver Transplanation in Jeju-do

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Aims: Jeju-do is far away south from the Korean peninsula. The prevalence of hepatocellular carcinoma (HCC) in Jeju-do is higher than that of the mainland in 2014 because of higher alcohol consumptions and a relatively higher rate of hepatitis B antigen positive. The patients who had unresectable HCC within the Milan criteria couldn't help going to larger institutions in metropolitan area to undergo liver transplantation. We have prepared for a set-up of living donor liver transplantation in Jeju National University Hospital (JNUH), Jeju-do science March 2014. Recently, we successfully performed the first LDLT in JNUH.
Methods: A male patient aged 34 was transferred to our emergency department due to gastric varix bleeding. He underwent endoscopic ligation for gastric varix bleeding, and then HCC was detected during an evaluation. He had chronic hepatitis B liver cirrhosis with HCC. A size of HCC was 4.8 cm in length. A donor aged 23 was male and his maternal cousin. There was no fatty change in the sonographic finding. An estimated remnant liver volume is 34.4% in the CT volumetry.
Results: We performed LDLT using right graft. The recipient's operation time was 421 minutes and the amount of an intraoperative blood loss was 3000 mL and 3 packs of red blood cell were needed to be transfused. Each donor and recipient was discharged in 11 and 19 days respectively without any postoperative episodes.
Conclusions: We are pleased to report our first successful case of LDLT in Jeju-do.
Keywords: Living donor liver transplantation, First case, Jeju-do

PE - 120

Prognostic Value of Change in Muscle Area on Serial Preoperative Abdominal CT Studies in Liver Transplantation

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Aims: Although pre-transplant sarcopenia predicts poor outcome, there are no studies about serial changes of muscle mass before liver transplantation. The purpose of study is to evaluate the changes in muscle, visceral and subcutaneous fat area during 1 year using serial preoperative CT studies before liver transplantation and to assess the association with prognosis of the patients.
Methods: A total of 72 patients (52 men, 20 women; mean age, 52.5years) underwent liver transplantation and also had serial CT scans preoperatively from May 1999 to November 2013 were included. At L3 body level, muscle and fat tissue area were measured by using Image J program (NIH, Bethesda, MD). Fat mass (FM), fat-free mass (FFM; muscle area), subcutaneous fat to muscle ratio (FMR) and visceral to subcutaneous adipose tissue ratio (VA/SA) were derived from area measured on CT scan. Then, patients' weight, body mass index (BMI), MELD score, FM index, FFM index, changes in FM and FFM (ΔFM and ΔFFM), FMR, and VA/SA were assessed to be correlated to the survival rates. Survival rates were calculated by using the Kaplan-Meier method. The Cox proportional hazards model with a stepwise procedure was used for the association between survival and variables.
Results: The 1-, 2-, and 3-year overall survival rates were 84.6%, 80.8%, and 78.2% for men, and 85.0%, 79.7%, and 79.7% for women, respectively. In the univariate analysis, MELD score (P=.007), FFM index (P=0.054), ΔFFM (P=.017), and ΔFM (P=0.133) were considered as possible related factors for overall survival. Multivariate analysis revealed that MELD score (P=.013) and ΔFFM (P=.039) were independent prognostic factors for overall survival.
Conclusions: Serial change in muscle area on CT studies during preoperative period may be associated with poor outcome in patients who underwent liver transplantation and can be considered as a selection criterion for a waitlist of transplantation.
Keywords: Liver transplantation, Sarcopenia, Survival, CT

PE - 121

De Novo Hepatitis B Virus Infection after Liver Transplantation in Hepatitis B Core-positive Recipients Using Hepatitis B Core-negative Grafts

Ion Buga, Hyeyoung Kim, Kwang-Woong Lee, Nam-Joon Yi, Hae Won Lee, YoungRok Choi, Suk-Won Suh, Jaehong Jeong, Suk Kyun Hong, Kyungchul Yoon, Hyo-Sin Kim, and Kyung-Suk Suh

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Hepatitis B core antibody-positive (HBcAb+) graft is known as a risk for de novo hepatitis B virus (HBV) infection in recipients after liver transplantation (LT). However, little is known aboutthe possibility or incidence of de novo HBV infectionsafter LT inhepatitis B surface antigen-negative (HBsAg-)/HBcAb+ recipients usingHBsAg-/HBcAb--grafts. The study was aimed at evaluating the prevalence of de novo HBV infection in HBsAg-/HBcAb+ recipients using HBsAg-/HBcAb- grafts. A retrospective review was performed with the records of 1,129 adult patients who underwent primary LT at a single institution in an HBV endemic area between January 2000 and December 2013.De novo HBV was defined as the detection of serum HBsAg+after LT. Total 111patients (9.8%) were HBsAg-/HBcAb+ recipients using HBsAg-/HBcAb- grafts. Among these, we excluded 33patients with HBsAg seroconversion before LT orless than 6 months follow-up after LT. Total 78 patients (6.9%) were reviewed for de novo HBV infection after LT. They underwent LT due to alcoholic liver cirrhosis (42.3%), hepatitis C related liver cirrhosis (24.4%), and cryptogenic liver cirrhosis (20.5%). Hepatocellular carcinoma was combined in 23 patients (29.5%). The mean follow-up after LT was 53.8 months(range, 8.0-164.0).De novo HBV infection was developed in 1 patient (1.28%). The patient was a 65-year old woman who underwent LT due to alcoholic liver cirrhosis on May 2012. De novo HBV was developed at 19 months after LT. There was no other risk factor for HBV infectionincluding transfusion. De novo HBV was not related to graft loss or death and welltreated with tenofoviruntil last follow-up (12 months). In conclusion, de novo HBV infections can be occurin HBsAg-/HBcAb+ recipients using HBsAg-/HBcAb- grafts, and caution is needed in these patients.

Keywords: De novo HBV infection, Liver transplantation, Core antibody, Viral hepatitis

PE - 122

Splenic Artery Steal Syndrome after Orthotopic Liver Transplantation

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Aims: To present successful treatment of post liver transplant non occlusive hepatic artery hypoperfusion syndrome presented by splenic steal syndrome (SASS) cases managed by splenic artery embolization. SASS is one of possible arterial complications after living donor liver transplantation. Material includes personal experience in diagnostics and treatment of this syndrome. In each case complication was suspected based on laboratory and ultrasound data and proved by angiography. Successful treatment was performed using splenic artery embolization.

Methods: From 2014 there are total of 13 liver transplantations were performed and we had 2 cases of SASS. All donor livers undergo biopsy and those biopsy tissues with no more than 10% steatosis could be eligible for transplantation.

Results: One of the most threatening complications of liver transplantation from a living donor is hepatic artery thrombosis. There are many possible causes of thrombosis including technical, and coagulation dysfunctions that will lead to the different level of graft disorders. However, in some circumstances other possible factors may induce arterial dysfunction due to functional features of visceral blood flow under established portal hypertension. SASS develops in 1-4% of post-transplant cases at early period after surgery from 2-5 days, and is characterized by re-distribution of blood supply from celiac trunk predominantly to splenic or gastro-duodenal artery. As a result of this phenomenon the linear and volumetric blood flow rates in the hepatic artery decreases leading to arterial ischemia of liver graft and might even lead to thrombosis. During this process the level of transaminases and bilirubin increases along with the Doppler ultrasound changes and CT-angiography data. The most dangerous consequence of SASS is the development of hepatic artery thrombosis (HAT) with the possible loss of transplant. The main reason of SASS development is hyper perfusion of the transplant. The timely diagnosis of the formidable pathologic syndrome is very crucial in order to avoid the loss of the graft.

Conclusions: It appears that patients with decompensated cirrhosis with long-time established portal hypertension should be carefully monitored early post-operative time after transplantation for any unexplained liver dysfunction confirmed with Doppler ultrasound, CT-angiography and coagulation abnormalities suggestive of SASS.

Keywords: Transplantation, Liver, Splenic, Embolization

PE - 123

LSRSL

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Aims: The patient with large splenorenal shunt (LSRS) is challenging at liver transplantation (LT), irrespective of organizing portal vein (PV) thrombus. Here, we report the clinical outcomes of 17 patients who received direct LSRS ligation during LT.

Methods: We reviewed patients who underwent LT and intraoperative direct ligation of LSRS between Jan. 2010 and Jun. 2013.

Results: Among 580 recipients, 17 patients underwent intraoperative direct ligation of LSRS. Pre-LT MELD score was 15.4 ± 6.6 (7 - 33). Main PV diameter on preoperative imaging was mean 7.6 ± 3.1 (3.0 - 13.9) mm. PV thrombectomy was done in 41.2% of patients (n = 7). Except one hospital mortality, 16 patients showed favorable outcome (94.1%). The mortality was related with sepsis, but not with liver dysfunction. There were 2 patients (11.8%) of major complication (Clavien-Dindo grade ≥ IIIa): splenic artery embolization for

massive ascites control (#1), and reoperation due to ligation of left renal vein instead of LSRS at the time of LT. Including the patient of splenic artery embolization (#1), massive and prolonged ascites after LT was in 23.5% of patients (n = 4) with small diameter of PV (< 7.5mm). They were living donor recipients, and not related with pre-LT ascites. Except the patient (#1), in the other three, ascites was tolerable and well controlled by conservative manage. After the patient (#1), we performed test clamp of LSRS before direct ligation in small diameter of PV, and applied PV pressure monitoring in patients who showed a sign of portal hypertension such as bowel edema. Three patients underwent total or partial ligation under PV pressure monitoring (within 8mmHg of pressure difference before and after ligation of LSRS). Total 16 patients have maintained normal liver function until last follow-up (94.1%).

Conclusions: Direct ligation of LSRS during LT is a safe and effective method to overcome the effects of LSRS. However, meticulous care is needed in isolation and ligation of LSRS. Selective simultaneous intraoperative portal pressure monitoring can be helpful for prevention of severe portal hypertension.

Keywords: The patient, With large, Splenorenal, Shunt

PE - 124

Cost-effectiveness and Convenience of Myrept® 500 mg Tablet in Recipients after Liver Transplantation

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Aims: Mycophenolate mofetil is the most common auxiliary immunosuppressant after liver transplantation to relieve calcineurin inhibitor related complications. There is one type of Cellcept® available, but Myrept® produced by Chong Kun Dang Company in Korea is available as 500 mg tablet as well as 250 mg capsule. However, there has been no clinical study to assess the feasibility of this generic product. Therefore, we aimed to evaluate the feasibility, cost-effectiveness, and convenience of Myrept® 500 mg tablet in recipients after liver transplantation.

Methods: A 24 week, phase 4, single center, open-label, non-comparative study was employed. A total of 50 patients were recruited. Acute rejection, changes in blood chemistry, white blood cell count, renal function, adverse drug reaction and other characteristics of the patients were recorded for 24 weeks. All enrolled patients and their grafts were survived within 24 weeks.

Results: There was no acute rejection. Mean GFR was 119.61 ± 76.52 ml/min at beginning of the study and reached 85.20 ± 23.70 ml/min after 24 weeks and showed a significant decrease overall ($p < 0.001$). Mean serum creatinine was 0.82 ± 0.27 mg/dL at beginning of the study and reached 1.01 ± 0.2 mg/dL after 24 weeks and showed significant increase overall ($p < 0.001$). However, there was no clinical significance. Nine patients (18.75%) had adverse drug reactions which had been commonly reported in other Mycophenolate mofetil generic products, and there was no serious one. These adverse reactions included gastrointestinal problems (nausea, vomiting, and abdominal discomfort), laboratory abnormality (mild increase of aspartate or alanine aminotransferase). The size of Myrept® 500 mg tablet is smaller than Myrept® 250 mg capsule (17.1 x 7.1 x 6.5 mm vs. 19.18 x 7.23 x 6.40 mm). When comparing the same dose, the cost is less expensive (1,344 Korean won vs. 1,792 Korean won for 500 mg).

Conclusions: Myrept® 500 mg tablet is feasible, cost-effective, and convenient in recipients after liver transplantation.

Keywords: Mycophenolate mofetil, Immunosuppression, Efficacy, Safety

PE - 125

Splenic Artery Embolization after Adult-to-adult Liver Transplantation

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Aims: Hypersplenism (thrombocytopenia, leukocytopenia, anemia) syndrome and ascites after orthotopic liver transplantation (OLT) are not rare complications. Commonly, such conditions treated by open splenectomy. But open splenectomy have many negative sides. As alternative surgical measure, splenic artery embolization (SAE) has been reported in literature. Our report presents the outcomes of SAE in 3 patients after liver transplantation with hypersplenism and/or ascites.

Methods: Between January 2013 and January 2016 in our Center we performed 32 OLT: 24 from living donor (1 - left lobe, 23 - right), 8 - from cadaver. Three patients after OLT received partial splenic artery embolization. Before OLT 2 recipients (both - female) with primary biliary cirrhosis, 1 - Hepatitis B Virus-related liver cirrhosis (male). Two patients after right lobe living OLT, one - cadaveric OLT. SAE in 3 cases were performed after 12, 8 and 6 month respectively. The indications for SAE was based on clinical examination, ultrasonography and CT (ascites, splenomegaly) and laboratory criteria (thrombocytopenia, when PLT<60x109/l, leukocytopenia, when WBC<2x109/l). Two recipient has leuko-thrombocytopenia and refractory ascites, 1 - only thrombocytopenia. SAE was performed via a percutaneous femoral artery approach 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 spleens were 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. After SAE: 2 patients had analgesia none-needed abdominal pain, 2 - had fever (max To was 38.5oC) during 3 days. The patients was discharged 6, 8, 9 days after SAE. One patient had perisplenic abscess without fever 1 month later after discharge.

Abscess was draned under ultrasound control. Than that patients discharged. One patient is died - after hepatic artery stenosis. Two patients after 1 year have normal leukocytes and thrombocytes levels.
Conclusions: Hereby, SAE, although limited by the minimal cases, is a safety minimally invasive methods for treatment hypersplenism and ascites of recipients after liver transplantations. Also, this method justified in patients under immunosuppression as alternatives to open total splenectomy.
Keywords: Splenic atery, Liver transplantation, Ascites

PE - 126

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 2013 and January 2016: 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: Immunosupression, Liver transplantation

PE - 127

Alterations of Hepatocellular Bile Salt Transporters and Effects of Immunosuppressants after Warm Ischemic Injury in Rats

Boldbaatar Minjuur, Hyeyoung Kim, Kwang-Woong Lee, Seung Cheol Oh, Geun Hong, Nam-Joon Yi, Hae Won Lee, YoungRok Choi, Suk-Won Suh, Jaehong Jeong, Suk Kyun Hong, Kyungchul Yoon, Hyo-Sin Kim, Kyung-Suk Suh

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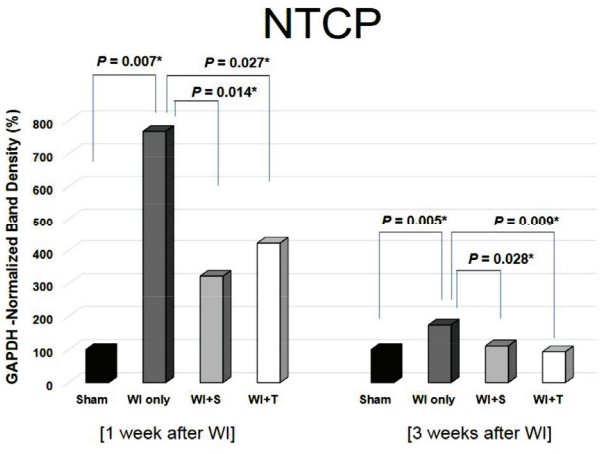
Aims: Warm ischemia (WI) and subsequent endogenous bile salt (BS) toxicity have been identified as important factors of intrahepatic bile duct strictures after liver transplantation. We aimed to identify the alterations of hepatocellular BS transporters and effects of immunosuppressants on it after WI in rats.
Methods: We designed warm ischemic rat model mimicking donation after cardiac death throughout specific operation: ligation of hepatic artery, clamping of portal vein during 30 minutes, and catheterization of bile duct. Male Sprague-Dawley rats (250-310 g) were used. After designed operations, 30 rats were divided into three groups: WI only (n=10), sirolimus (WI+S, n=10), and tacrolimus (WI+T, n=10). They were sacrificed for procurement of liver at 1 week and 3 weeks (on halves). As control, 6 rats underwent sham-operation. Using liver tissue, protein expression of hepatocellular BS uptake (NTCP, OATP1B3) and export (MRP2, MDR2) transporters were quantitatively measured by Western blot.
Results: At 1 week after WI, all 4 transporters were significantly increased (mean 767.6% in NTCP, 122.1% in OATP1B3, 530.5% in MRP2, and 282.7% in MDR2; all p=0.007) compared to control (100.0%). At 3 weeks, all transporters were decreased again. However, NTCP was still significantly high (mean 174.0%; p=0.005), and other transporters showed no significant differences compared to control (p=0.095). In rats treated with sirolimus or tacrolimus, NTCP was significantly reduced at 1 week (p=0.014 in WI+S vs. 0.027 in WI+T) and 3 weeks (p=0.028 vs. 0.009), compared to WI only group. In OATP1B3, there was no significant effect of both immunosuppressants. In export transporters, MRP2 was significantly reduced at 1 week (both p=0.014), and MDR2 was at 3 weeks (both p=0.047).
Conclusions: In conclusion, hepatocellular BS transporters are significantly increased after WI in rats. Sirolimus and tacrolimus have buffering effects on these WI induced alterations of BS transporters.



Keywords: Hepatic bile salt, Bile acid transporter, Transporter expression, Warm ischemic injury, Non-heart beating donor, Liver transplantation, Tacrolmus, Sirolimus, Rat, Animal study

PE - 128

The Correlation between Pre-operative Volumetry and Real Graft Weight: Comparison of Two Volumetry Programs

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Introduction: Accurate pre-operative assessment of graft volume is important for donor safety and recipient outcome. Nowadays, there are several clinically available volumetry programs. There has been not so much report to the accuracy of each programs. In this study, we aimed to evaluate the accuracy of two volumetry programs in preoperative graft estimation compared with real graft weight.
Methods: From October of 2013 to August of 2015, there were performed 274 cases of right living donor liver transplantation in SNUH, Seoul, Korea. Among them, 215 patients in whom both pre-operative volumetry data and real graft weight information were available were included in this study. We had used 'Rapidia®' until April of 2014, and then 'Dr.Liver®' has been exclusively used. 107 patients belonged to Rapidia®' group and another 108 patients belonged to Dr. liver group. Real graft weight was measured during bench surgery. The difference between volumetry and real weight was graded into minimal difference (≤10%) and big difference (>10%). We compared the correlation coefficient and degree of difference between two different programs.
Results: The correlation coefficients of 'Rapidia®' (0.836) was lower than that of 'Dr.Liver®'(0.868). The cases measured by 'Rapidia®' showed minimal difference in 39 cases (38.6%) and big difference in 62 cases (61.4%). However, the cases measured by 'Dr.Liver®' showed minimal difference in 59 (54.6%) cases and big difference in 49 (45.4%). 'Dr.Liver®' showed significantly more minimal difference than 'Rapidia®' (p=0.026).
Conclusion: Comparing the results of both programs, 'Dr.Liver®' showed better correlation with real graft weight than 'Rapidia®'. It may be related with the difference of measurement methods between two programs. More precise method to predict real graft weight should be investigated.

PE - 129

Liver Transplantation Utilizing a Lacerated Liver

Jang Yong Jeon

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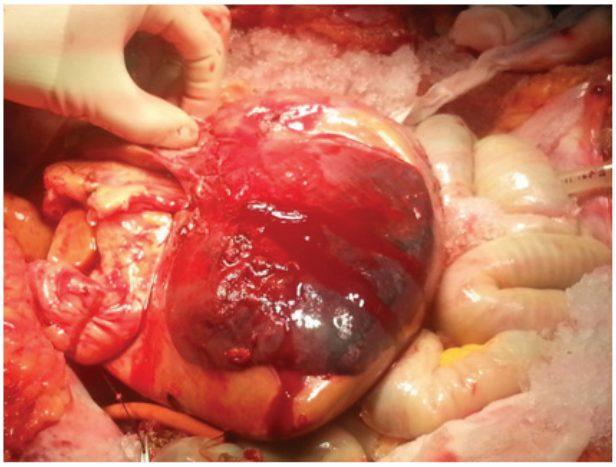
Aims: Using lacerated liver for liver transplantation can add an option to the extended donor criteria. We present an liver transplantation case using a lacerated liver and review of the literarture for reported cases.
Methods: We used a II-III grade lacerated liver from a 52 year old brain dead patient caused by traffic accident.
Results: The liver had grade II-III lacerations in the sement 5, 6 and 7. Lacerations were managed by Argon, bipolar, sealants and stitching. The liver was transplanted to a 48 year old man suffering from alcoholic liver cirrhisis with uncontrolled ascites. On POD#1 re-exploration was done because of bleeding from drain. The bleeding was on liver laceration area. the 6 month follow up was uneventful. The reported complications of liver transplantation using lacerated liver were primary nonfunction, or poor function, liver abscess, biloma,



and subhepatic hematoma.
Conclusions: With meticulous management lacerated livers can be transplanted successfully by experienced liver

PE - 130

De Novo Malignancy within One Year after LDLT : Case Report

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Aims: Biliary obstruction is a common morbidity after liver transplantation. The anastomotic failure of biliary reconstruction is the leading cause. When the patient with hepatocellular carcinoma (HCC) underwent liver trasplantation and developed a jaundice, the recurrence of HCC is suggested as the main cause.
Methods: Here we describes a case of biliary obstruction due to pancreatic head cancer at 11 months after LDLT. The patient was a 54-year-old male with HBV related cirrhosis and hepatocellula carcinoma (HCC) within Milan criteria. Our patient previously underwent liver resection for HCC two times in 1998 and 2002. Recurrence of HCC revealed and LDLT using the right lobe from his 23-year-old daughter was performed in December 2008. Immnosuppressive treatment was administered with basiliximab, tacrolimus, corticosteroids and mycophenolate mofetil. He discharged on postoperative 28th day with uncomplicated course.
Results: At eleven months after operation, the patient showed icterus. Ampullary stricture below the anastomosis site was found by MRCP and finally diagnosed in adenocarcinoma with endoscopic biopsy. Pylorus-preserving pancreaticoduodenectomy (PPPD) was performed for complete resection of pancreatic head cancer on 14 months after LDLT. The patient revealed favorable outcomes except for superior mesenteric arterial (SMA) pseudoaneurysmal bleeding controlled by endovascular graft postoperatively. However, the patient died from recurred pancreatic head cancer two year after LDLT.
Conclusions: Our experience suggest that high suspicion of de novo malignancy is needed for the patient with HCC who has undergone liver transplantation.
Keywords: Liver transplantation, Denovo malignancy

PE - 131

Recent Advancements in the Pediatric Liver Transplantation: A Single Center Study of 237 Patients Over 27 Years

Sung-Woo Ahn[1], Nam-Joon Yi[1], Kyung-Chul Yoon[1], Hyo-sin Kim[1], Suk-Kyun Hong[1], Hyeyoung Kim[1], Jin-Young Choi[1], Joon Koo Han[2], Min uk Kim[2], Hyo-Cheol Kim[2], Kwang-Woong Lee[1], Kyung-Suk Suh[1]

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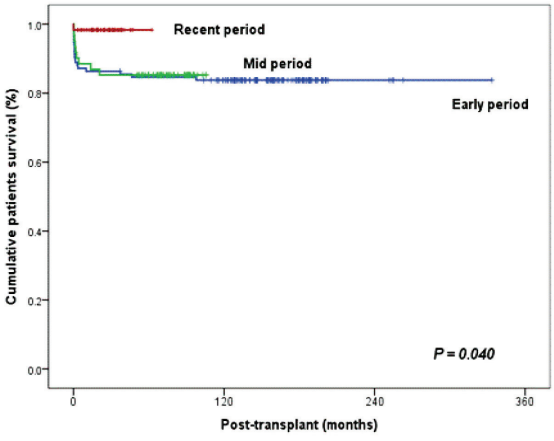
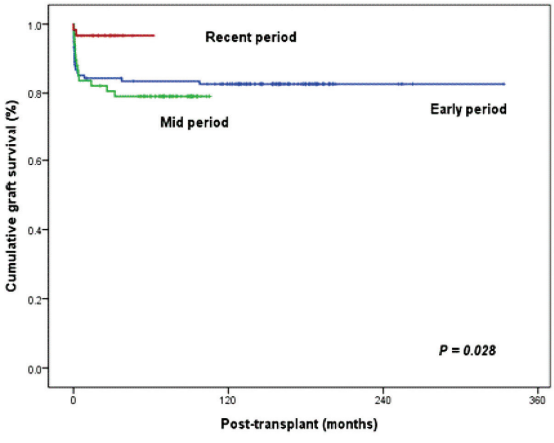
Aims: Pediatric liver transplantation (PLT) has been the key therapy for end stage liver disease and the outcome has been excellent. However, still surgical complication associated with small recipient is the main cause of graft loss. In the present study, we assessed recent advances in outcome of PLTs through our experience.
Methods: A total of 237 PLTs performed between Mar 1988 and July 2015 were analyzed. Three chronological periods were investigated: the initial period (1988-2007, n=117), the mid-term period in which our PLT management protocol was settled down (2008-2011, n=61), and the period in which surgical procedures were refined for small children (2012-2015, n=59).
Results: The grafts' (84% vs. 82% vs. 98%) and patients' (84% vs. 87% vs. 98%) survival have been improved (p<0.05), whereas the proportion of Child class C (12% vs. 21% vs. 34%), the proportion of deceased donor (25% vs. 41% vs. 54%), and split PLT (15%vs. 20% vs. 39%) increased (p<0.05). The incidence of surgical complication has been improved, especially in hepatic artery (4% vs. 12% vs. 0%) but there was no significance. ABO incompatible PLT has introduced on the last period (9%).
Conclusions: The quality of the PLT has recently been standardized through a large volume of experience, and the operation has been proven to improve the survival outcome. However, a constant evaluation of our experience is critical for further progress.
Keywords: Pediatric, Liver transplantation, Survival





PE - 132

Long-term Cosmetic Outcomes of Wound Following the Different Minimally Invasive Incisions for Living Donor Hepatectomy in Liver Transplantation

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Aims: Reviewed the long-term cosmetic outcomes of the different types of wound incision.
Methods: 121 Living donors underwent donor hepatectomy for LDLT from September 18th 2006 to December 6th 2013 were included. They were divided into 4 groups according to the incisional types; inverted L upper (n=78 the L group), upper midline (n=35, the U group) and transverse (n=8, the T group). Wound cosmetic outcomes were evaluated mean 458 days after operation using the Vancouver Scar Scale.
Results: The T group had better cosmetic outcomes; VSS median of 4.5, 5.0, 6.0 and 7.0 in T, MB, L and U groups respectively. Pigmentation (P=0.153), vascularity (P=0.219), pliability (P=0.336) and wound height (P=0.639) were not different according to the groups. Hypertrophic scarring and Keloids occurrence was lower in T group: 1 (12.5%) in T group, 10 (28.6%) in U group and 19 (24.4%) in L group (P=0.033) (Table 1). The location of scarring was usually in midline incisional site. The distribution of scarring was even in the transverse incision, but it was occurred a little more in the upper 1/3 and the lower 1/3 in midline incision.
Conclusions: General long-term cosmetic outcomes were similar following the different minimally invasive incisions. Hypertrophic scar and Keloids occurrence can be decreased in the transverse incision.
Keywords: Liver transplantation, Different minimally Invasive incisions, Donor

PE - 133

Fate of Potential Living Donors for Liver Transplantation

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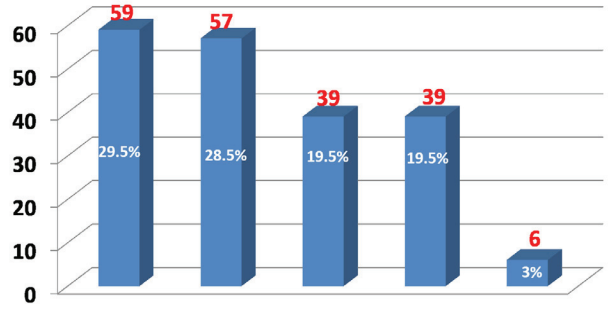

Republic of China, [2]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

Aims: In this study, we aimed to elucidate the fate of potential live liver donors.

Methods: From July of 2011 to June of 2013, 372 potential donors were evaluated for 302 matched recipients. Data was prospectively collected.

Results: Among 302 recipients, 209 patients received LDLT finally. Among 302 recipients, 53 recipients (17.5%) had more than 1 potential donor. 64.8% of donors was male and 53.5% was children of the recipients. Among 372 potential donors, 209 donors (56.2%) finally received donor hepatectomy for living donation. 159 cases (42.7%) were excluded for various reasons. Among 159 excluded cases, 87 cases were excluded due to donor reasons. The other 72 cases could not donate due to recipient reasons e.g. death, infection or Deceased donor LT. Donor reasons for exclusion consisted of withdrawal of consents (n=25, 28.7%), medical problems (n=24, 27.6%), small remnant volume (n=17, 19.5%), and others (n=21, 24.1%). The main reasons for donor exclusion were medical problem and withdrawal of consent. Therefore, thorough medical clearing and careful examination for donor voluntarism are important in donor evaluation process.

Conclusions: The main reasons for donor exclusion were medical problem and withdrawal of consent. Therefore, thorough medical clearing and careful examination for donor voluntarism are important in donor evaluation process.

Keywords: Donor, Liver transpantation

PE - 134

Pre-transplant Live Donor Evaluation Protocol for Liver Transplantation at a Single Major Center

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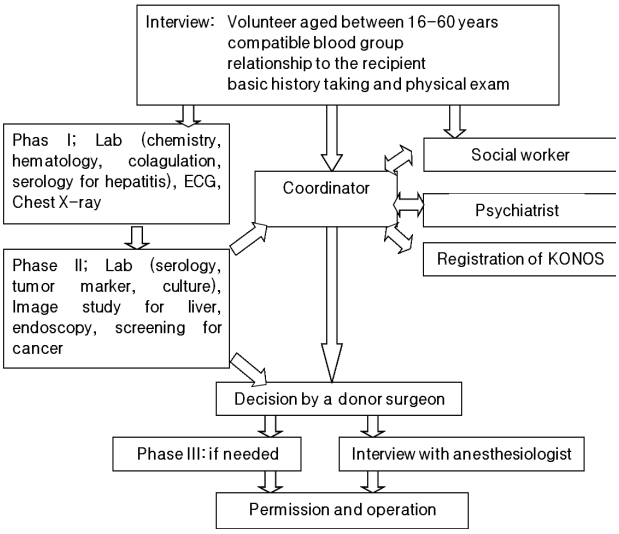
Aims: Introduce a pre-transplant donor evaluation protocol for liver transplantation.



Methods: At Step1, the general condition of a potential donor is evaluated. The assessment includes the medical history, body size, psychosocial circumstance, and basic blood and urine profile. Age is usually 16-60 years. A relationship between the recipient and donor should be within the third degree of consanguinity or an intense emotional relationship judged by ethical board of local committee. At Step 2, potential donor undergoes tests for viral and neoplastic disease and imaging studies for anatomy and quality of the liver. At Step 3, the invasive procedures including liver biopsy and additional consultations required to investigate the potential problems discovered during phases 1 and 2 are done. A preoperative liver biopsy was applied to the moderate steatosis from imaging studies. The volume of the liver is calculated by CT imaging. The biliary anatomy is confirmed by MRCP and primovist MRI. The presence of mild systemic diseases (e.g., well-controlled hypertension or diabetes) is not necessarily a contraindication. The donors are advised to stop smoking and drinking. The remnant liver volume ≥ 30% of the whole liver is recommended. If macrovesicular steatosis is ≥ 10%, we do liver biopsy and recommend diet control. Donors with a GRWR > 0.8% were generally accepted. Minimal variation of the anatomy of the liver has been accepted. If the whole process has been accepted, a donor surgeon decides operation's type.

Results: There was no mortality and the overall morbidity was < 6.0%, including 0.9% of major complications (> grade III). Conclusions In conclusion, meticulous donor evaluation is important for the successful LDLT.

Keywords: LDLT, Evaluation protocol

PE - 135

Portal Vein Complication after Living Donor Right Hepatectomy

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Purpose: Living donor hepatectomy may carry a significant risk of

morbidity and mortality for the otherwise healthy donor. Portal vein (PV) complication after donor hepatectomy is rare but cause severe sequelae without proper management. This study intended to assess incidence and treatment of portal vein (PV) complication after living donor right hepatectomy.

Methods: This study analyzed 2997 cases of living donor right hepatectomy from July 1997 to December 2014 at Asan Medical Center regarding on portal vein complication.

Results: Male and female were 2072 (69.1%) and 925 (30.9%), respectively. Mean donor age was 27.5±8.1 years old. Mean body mass index was 22.67±2.75. Type 1, 2, 3, and 4 PV anomaly were 2769 (92.4%), 99 (3.3%), 127 (4.2%), and 2 (0.1%), respectively. PV stenosis (>50% narrowing of PV diatmeter) occurred 19 cases (0.6%). Incidence of PV stenosis was occurred in 0.3% in type 1, 3% in type 2, 5.5% in type 3, and 0% in type4 (P<0.001). Among 19 PV stenosis donors, PV stent insertion was performed in 7 cases (0.2%) which occurred 2 in type 1 (0.1%), 0 in type 2 (0%), 5 in type 3 (3.9%), and 0 in type 4 (0%) (P<0.001). One patient with type 3 PV anomaly who performed end to end anastomosis of PV to make one orifice in graft side PV during donor right hepatectomy intra-operatively inserted PV stent at post-operative 2 days due to PV thrombosis and stenosis. Other 6 patients who inserted PV stent underwent the procedures percutaneously from postoperative 16 to 70 days. All PV complication donors had no long-term sequelae and are alive.

Conclusion: Portal vein complication after donor right hepatectomy is rare but require proper management. Type 2 and 3 portal vein anomaly donors have a tendency to occur portal vein complication after donor right hepatectomy. Especially donors with type 3 portal vein anomaly should be cautiously harvested graft intraoperatively and followed with image studies.

PE - 136

Salvage Liver Transplantation for Hepatocellular Carcinoma after Laparoscopic or Open Hepatectomy

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Purpose: A salvage liver transplantation (LT) strategy that has been shown to be comparable to primary LT, the patient can avoid life-long immunosuppression. A previous hepatectomy may increase surgical difficulty by creating intraabdominal adhesions. Laparoscopic hepatectomy (LH) may reduce such technical consequences, but its effect on subsequent LT has not been reported. We study the operative results of LT after laparoscopic or open hepatectomy (OH).

Methods: From January 2010 to December 2014, 111 salvage LT were performed, 10 following prior LH and 101 following prior OH. Indication for the LT was recurrent HCC in all cases.

Results: In the LH group, absence of adhesions was associated with straightforward access to the liver in all cases. In the OH group, 101 patients required long and hemorrhagic dissection. Median durations of the whole LT were 674 and 804 min in the LH and OH groups, respectively (p<0.05). Mean packed RBC transfusions during LT were 3 and 14 U in the LH and OH groups, respectively (p<0.05). Median post-operative length of stay was 19 and 23days in the LH and OH groups, respectively (p>0.05). In-hospital mortality was 2.9% (n=3) only in OH group.

Conclusion: In our study, salvage liver transplantation after laparoscopic hepatectomy for HCC is advantageous to open surgery in terms of operative time, blood loss and transfusion requirements.

PE - 137

Short Term Life Style Modification Can Improve Fatty Liver in Donor Candidates

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Purpose: It has been known that mild fatty liver grafts (<30%) do not have a significant impact on liver function and liver regeneration. However, NAFLD is related NASH and its general incidence has been reported upto 50% in general population. To reduce both donor and recipient's risk, we have considered the donor's liver with even mild fat fraction and inflammatory changes in preoperative liver biopsy.

Methods: MRI is used for the decision for undergoing a biopsy and measuring of fat fraction. Even though fat fraction is mild, if it is greater than 5-10%, biopsy is undertaken considering the donor's age and GRWR, the recipient's liver function, and emergency status to check for NAFLD, NASH. If the above results are mild and the recipient's status is not an emergency, we encouraged the donor to exercise. Follow up MRI and biopsy was done to check the changes in fat fraction and once again the recipient's emergency status was checked to decide whether or not to proceed with the surgery. Moderate or severe degree of fat fraction were determined to be unsuitable for donation.

Results: A total of 776 patients underwent donor workup for 588 patients waiting for liver transplantation between July of 2011 and June of 2015. A total of 65 patients had more than 5% fatty liver in CT or MRI, and from the 65 patients 19 patients had moderate to severe fatty liver and were determined to be unsuitable for donation. Out of the 45 patients who had mild fatty liver 13 patients' biopsy showed more than 10% macrovesicular change and we encouraged life style modification for those 13 patients. Except only one patient, 12 patients were improved their fat fraction and biopsy result. About 45 to 119 days of life style modification by diet and exercise. these patients lost an average of 5.2 kg. Macrovesicular fatty change was reduced from 10-35% to 0-10% of these patients. Weight loss resulted mostly in reduction of macrovesicular change and also in reduction of inflammatory, fibrotic changes.

Conclusion: In most of these patients about 2 to 3 months of life

style modification resulting in weight loss lowered the fat fraction and changes of inflammation, fibrosis. Thus, it is important to educate and prepare the patients who are preparing for liver donation for liver transplantation.

PE - 138

Graft Versus Host Disease (GVHD) after Liver Transplantation (LT) Focused on Deceased Donor LT (DDLT) : A Propensity Score-matched Study

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Purpose: Graft versus host disease (GVHD) is a rare (0.1-1%) but severe complication after liver transplantation. Due to rarity, few studies have been proposed the risk factors and yet they have been inconclusive.
Methods: We performed a retrospective analysis of 1700 liver transplants (living donor : deceased donor=1190 : 510) in Seoul National University Hospital in Korea, from March 1988 to October 2015, over a period of 27 years.
Results: Six patients (6/1700, 0.35%) with histologically diagnosed GVHD were included. One patient received living donor LT (LDLT) and found to be one-way HLA matching, which is generally known to be significant risk factor. Focusing on the other five DDLT cases, each of these five cases was matched to four controls based on the blood group, sex, and age difference between recipient and donor. Analyses were performed to identify risk factors associated with the development of GVHD after DDLT. Higher pre-LT AFP was identified to be a risk factor (p=0.002), until accompanying hepatocellular carcinoma identified not to be the risk factor (p=0.252). Although not statistically significant, operation time was potential risk factor (p=0.051). GVHD has been extremely rare and difficult in diagnosis and, what is more, fatal in outcome.
Conclusion: Considering these risk factors when allocating, we may reduce further incidence of GVHD in DDLT.

PE - 139

A Case of Deceased Donor Liver Transplantation Using Renoportal Anastomosis in Patients with Diffuse Portomesenteric Thrombosis

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Purpose: Adequate portal inflow is essential for successful liver transplantation. However, portal vein thrombosis (PVT) is not uncommon in end stage liver disease and PVT was considered as relative contraindication of liver transplantation in past because of technical difficulties that induced an increased intraoperative bleeding and an inability to establish adequate portal inflow. However, with technical improvement such as venous eversion thrombectomy, vascular interposition grafts, and use of portal vein collaterals, PVT has not been accepted as contraindication of liver transplantation any more. Here, we describe a successful case of deceased donor liver transplantation (DDLT) with renoportal anastomosis in patient with diffuse portomesenteric thrombosis.
Methods: A 67-year-old man was diagnosed with alcoholic liver cirrhosis 17 years ago and had been followed-up regularly. Segmental PVT was developed 8 years ago and had been extended to superior mesenteric vein and splenic vein. The patient had undergone endoscopic esophageal variceal ligation twice for hematemesis and paracentesis frequently for ascites control. Preoperative CT scan revealed features of diffuse mesoportal thrombosis, splenic vein thrombosis with splenomegaly, cavernous transformation of portal vein, and large splenorenal shunt. This patient underwent deceased donor liver transplantation. Inferior vena cava was anastomosed with piggy-back technique and portal flow was obtained from left renal vein (eno-to-end anastomosis). The anastomosis of hepatic artery and bile duct was performed rountine manner.
Results: Introperative and postoperative Doppler sonography showed adequate portal flow and liver function was improved gradually. CT which performed at postoperative 10 days and 3 months showed adequate perfusion of portal flow from left renal vein and liver function has been preserved stably.
Conclusion: Renoportal anastomosis is one of the alternative methods for portal flow reconstruction in patients with diffuse portomesenteric thrombosis and splenorenal shunt.

PE - 140

Dual Stent Placement for Suprahepatic Inferior Vena Cava Stenosis after Deceased Donor Liver Transplantation with Piggy-back Technique

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Purpose: Outflow obstruction after liver transplantation is uncommon but can have serious effects on the outcomes. Outflow obstruction caused by inferior vena cava (IVC) compression or kinking can be occurred sometimes after side-to-side piggy-back technique using large liver graft. Recently, outflow obstruction has been treated successfully by stent placement. However, IVC stent placement has some problems due to the overlapping IVC and the angle of approach in cases of side-to-side piggy-back technique. Herein we have reported successful treatment of outflow obstruction caused by suprahepatic IVC stenosis after deceased donor liver transplantation with side-to-side piggy-back technique.
Methods: A 34-year-old woman underwent DDLT for alcoholic liver cirrhosis. The patient was slim with BMI 19. However, she had a large amount of ascites which was not controlled by diuretics and her liver was hypertrophied (2372 g). Although graft was relatively large weighted 1950 g, intraabdominal space was sufficient to implant

graft. IVC anastomosis was performed by side-to-side piggy-back technique and other procedures were performed routinely without problem. After transplantation, laboratory test had been improved gradually and patent vascular flow was observed in Doppler ultrasound exam. However, abdominal drainage was significantly increased over 5 L/day. Computed tomography was performed on postoperative day 7 and suprahepatic IVC stenosis was shown. Venography showed suprahepatic stricture by IVC kinking. Measured pressure gradient between infrahepatic and right atrium was 17mmHg and between hepatic vein and right atrium was 14mmHg. Self-expandable metallic stent was placed across the stenotic area of recipient's suprahepatic IVC through right internal jugular vein and additional stent was placed across anastomosis to right hepatic vein through right femoral vein to prevent compression of hepatic vein outlet by IVC stent.

Results: After stent placement, pressure gradient was improved and there was no procedure-related complication. The amount of ascites and diuretics requirement was significantly decreased after procedure.

Conclusion: Percutaneous stent placement is a safe and effective procedure in patient with outflow stenosis, however this procedure should be performed with a well-designed plan.

PE - 141

Long-term Outcomes of Pediatric Living Donor Liver Transplantation Using Pure Laparoscopic Donor Hepatectomy

Wan-Joon Kim, Woo-Hyung Kang, Seok-Hwan Kim, Hwui-Dong Cho, Jae-Hyun Kwon, Eun-Kyoung Jwa, Ki-Hun Kim

Department of Hepato-biliary and Liver Transplantation, Asan Medical Center, University of Ulsan College of Medicine, Korea

Purpose: There were some papers about the CO2 gas which using it during laparoscopic surgery has adverse effect on survival of graft. Then we want to evaluate the effect of laparoscopic circumstance on the aspect of transplantation surgery.

Methods: Between May 2008 and June 2014, there were 27 children age ≤ 17 years who received a liver transplant. Demographic characteristics, patient survival, rejection episodes, and complications were recorded. Statistical methods included simple descriptive analysis and Kaplan-Meier method. Statistical significance was defined by P≤0.05

Results: The mean patient age was 1.6±1.61 and was 11 male (39.3%) and 16 female (57.1%). Mean total bilirubin was 13.8±9.5 and mean INR was 1.44±0.57. Biliary atresia was the most common cause of end-state liver disease and mean PELD score was 14.5±7.3. 24 patients were performed Laparoscopic Left lateral sectionectomy and 3 patients were performed Laparoscopic Left hepatectomy. The most common cause of complication was acute cellular rejection (25.9%). Mean follow-up period was 59.2 months (range 4.2-93.1). There were not reported on In-hospital mortality and all patients were survived until end of follow-up date. (Dec. 2015).

Conclusion: Laparoscopic donor hepatectomy was feasible and safe tool for living-liver transplantation and may provide excellent graft outcomes in children. The circumstance of laparoscopic surgery has not adverse effect on recipient of living donor liver transplantation.

PE - 142

Liver Transplantation in a Small Volume Center: Initial Outcome

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Purpose: Case volume is popularly being used as a quality indicator for high-risk and complex surgical procedures. Especially, liver transplantation surgery is a challenging procedure that is associated with high perioperative morbidity and mortality, due to patient comorbidities and technical demands of the procedure. So it is justifiable to perform such a procedure in high-volume procedure centers. However, small volume center can provide a service for a local population that would have limited opportunity for LT in large volume center due to the cost or poor conditions for transfer. Herein, we report our initial experiences and outcomes of liver transplantation as a small volume center.

Methods: In our hospital, we performed 13 liver transplantations from July 2014 to January 2016. Among 13 patients, we performed 9 deceased donor liver transplantations (DDLT) and 4 living donor liver transplantations (LDLT). Indications for LT were primarily hepatitis B (n=7), alcoholic (n=5) and autoimmune hepatitis (n=1). Among 13 patients, 3 patients were accompanied by HCC and one patient was accompanied by intrahepatic cholangiocarcinoma. For deceased donors, inferior vena cava anastomosis was performed by piggy-back technique and for living donors, modified Rt. graft was used with middle hepatic vein reconstruction by Dacron graft. Liver transplant patients were treated in the ICU postoperative day 6. The immunosuppressant regimen consisted of conventional triple regimen (FK506, MMF and steroid).

Results: In this series, the 90-day mortality was 0%. Also, there was no graft failure in 13 recipients. There were 2 patients mortality in the follow up period. The causes of mortality in each patient were cardiac arrest on postoperative 4 months and HCC recurrence on postoperative 14 months. Three patients (23%) required biliary stent due to bile duct anastomosis site stricture. There was not any vascular complication during postoperative period. The acute cellular rejection (ACR) was occurred in 2 patients, and they all recovered from ACR by steroid pulse therapy. In LDLTs, there were no donor mortality and postoperative complication.

Conclusion: Although there is no long-term data yet, liver transplantation results in this series as a small volume center were comparable. Other major hepatobiliary procedures can help the surgeons maintain their operative skills. A smaller LT program may require more efforts, but it can provide a good service for a local population.

Liver, Infectious Disease

PE - 143

Case Series of Hepatitis A Virus Infection Associated with Hemophagocytic Lymphohistiocystosis Presenting as Liver Failure

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Virus-associated hemophagocytic syndrome (VAHS) is reported to be a rare but serious complication in hepatitis A virus infections. High fever, cytopenia, elevated soluble IL-2, elevated ferritin, splenomegaly were initial important findings of VAHS which are not rare in patients with acute hepatitis A. Although hemophagocytosis associated with other types of virus infections is fatal, patients with HAV-AHS recovered well with timely steroid & immunosuppressive treatment. However, there is no consensus in the literature regarding the optimal treatment of VAHS until now.

Here in, we encountered four patients with hepatitis A virus-associated hemophagocytic syndrome (HAV-AHS) who completely recovered with timely steroid treatment.

Keywords: Hepatitis A, Lymphohistiocytosis, Hemophagocytic, Steroids

PE - 144

A Rare Case of Acute Myocardial Infarction Due to Septic Emboli Caused by Klebsiella Pneumoniae Liver Abscess

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Aims: Invasive Klebsiella pneumoniae syndrome has metastatic complications such as bacteremia, meningitis, endophthalmitis, pulmonary thromboembolism, and necrotizing fasciitis. We presented a rare case of acute myocardial infarction due to septic emboli caused by K. pneumoniae liver abscess.

Methods: A 52-years-old male patient admitted because of febrile sensation of 10 days duration. He had a history of diabetes mellitus and hypertension 25 years ago. On admission, BP was 110/70 mmHg, HR 109 beats/min, RR 20 breaths/min, and BT 36.6℃. Initial ECG showed sinus tachycardia. Initial laboratory findings were; WBC 18,910/mm3, PLT 297,000/mm3, AST/ALT 63/96 IU/L, T-bil 1.04 mg/dL, and CRP 22.06 mg/dL. Abdominal CT showed huge liver abscess at right hepatic lobe. Empirical antibiotics (ceftriaxone and metronidazole) was started. On 2nd day, he complained dyspnea and hypotension occurred. Laboratory findings were; WBC 44,610/mm3, PLT 55,000/mm3, AST/ALT 836/465 IU/L, T-bil 2.91 mg/dL, CRP 25.30 mg/dL, and procalcitonin 147 ng/dL. Chest X-ray showed pneumonia in both middle and lower lung zones. Percutaneous drainage was done. On 3rd day, he complained dyspnea and chest discormfort. Troponin-I was 8.773 ng/dL, ECG showed ST elevation at precordial lead, and TTE showed decreased anteroseptal & apical wall motion. We consulted to cardiology and concluded that acute myocardial infarction due to septic emboli. Cardiologists recommended that keep antibiotics and consider coronary angiography after improvement of septic condition. On 5th day, initial blood culture resulted K. pneumoniae, and liver abscess culture resulted same pathogen, K. pneumoniae. Now he slowly recovered and was scheduled to coronary angiography.

Conclusions: Invasive Klebsiella pneumoniae syndrome has poor prognosis, so earlier diagnosis and appropriate antibiotic treatment combined with percutaneous drainage increases chance of survival.

Keywords: Acute myocardial infarction, Klebsiella pneumoniae, Liver abscess

PE - 145

Demographic Profile, Imaging Findings and Treatment Outcomes of Hepatobiliary Ascariasis

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Aims: Ascariasis is the most common helminthic infection in humans. It is very frequent in developing countries such as Asia due to poverty, overcrowding and poor sanitation. A serious manifestation of infection is hepatobiliary ascariasis due to potential for complications. The aim of this study is to describe the demographic profile, risk factors, clinical presentation, usual diagnostic findings and treatment options of hepatobiliary ascariasis patients in the Philippines.

Methods: This is a retrospective cross-sectional study of all patients diagnosed with hepatobiliary ascariasis from January 2005 to February 2016. Diagnosis of hepatobiliary ascariasis were confirmed by findings and signs of worms in the biliary tract through ERCP or imaging findings. Data were encoded using MS Excel and analysis done by SPSS.

Results: Among 23 patients, mean age was 39.9. Majority were female patients(82.6%). From available data, all patients earned less than 100,000/ year and finished only up to High School. 13% had previous sphincterotomy while 8.7% had previous gallbladder surgery. Common indications include RUQ pain or biliary colic (56.5%), epigastric pain (21.7%) and diffuse abdominal pain (21.7%). For complications, 26.1% had obstructive jaundice, 4.3% had acute cholangitis, and 8.7% had acute pancreatitis. Usual initial test was ultrasound mostly showing a tubular filling defect at the bile ducts (78.2%) 20 patients underwent ERCP with cholangiogram showing a tubular filling defect for 18 patients, a dilated common bile duct and a patulous ampulla for some. Majority of worms were removed by basket extraction (73.9%). 73.9% showed dead worms with mean procedure time of 34.6 minutes.

Conclusions: Hepatobiliary ascariasis is a serious manifestation of ascariasis infection. A thorough history for risk factors and examination with the help of imaging findings can help us in adequately diagnosing this condition. Importance of adequate treatment with extraction of worms should be emphasized to prevent severe complications of disease.

Keywords: Hepatobiliary ascariasis, Ascaris worms, Biliary ascariasis, Retrospective

NAFLD, Basic

PE - 146

Transcriptomic Approach for Non-alcoholic Fatty Liver Disease Using a Systems Biology Technique

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Aims: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease (CLD) with an estimated 30% prevalence in the US for NAFLD and 3-5% for NASH. However, the pathogenesis is poorly understood and probably multifactorial and additionally how best to manage comorbidities such as dyslipidemia, obesity, and metabolic syndrome is unclear. Moreover, conventional functional and genetic attempts have failed to discover outstanding disease-causing factors due to the complex nature of the disease.

The main goal of our study is to identify potential biomarkers of the disease and to characterize genetic markers that can modulate such genes to ultimately lead to the discovery of individual-specific drug targets.

Methods: In a prospective cohort study, we collected human liver tissue samples and subjected them into the expression quantitative trait loci (eQTL) analysis by generating genome-wide gene expression and genotyping data. Preliminarily, it was analyzed by means of RNA-sequencing pilot experiments using 4 healthy control liver tissues and 6 NAFLD liver tissues. Volcano plot and heatmap of gene expression data were generated for differentiation of the relative expression levels of genes.

Results: Genome-wide transcription expression distribution demonstrated that the 10 samples display similar expression pattern after normalization. Differentially expressed genes are selected by multiple-corrected, significant changes between the healthy and NAFLD tissue expressions. Expression of significantly enriched genes was shown in the gene ontology analysis. Three biological pathways including defense response, intrinsic to plasma membrane, and vacuole were identified as candidate biomarkers for discriminating NAFLD subjects from healthy population.

Conclusions: In this pilot study, we found causal genes that confer disease susceptibility and genomic variants that directly regulate the causal gene expression. These results will provide new insight into the molecular and functional mechanisms of NAFLD and potentially lead to the discovery of new biomarkers for NAFLD.

Keywords: Non-alcoholic fatty liver disease, RAN-seq, Biomarker

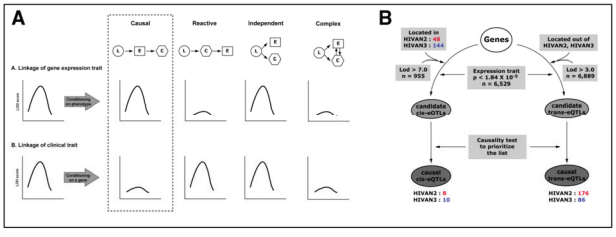

Figure 1. eQTL approach. (A) Schematic diagrams depicting the causality test. (B) Main steps of discovering causal genes for the HIVAN eQTL project.

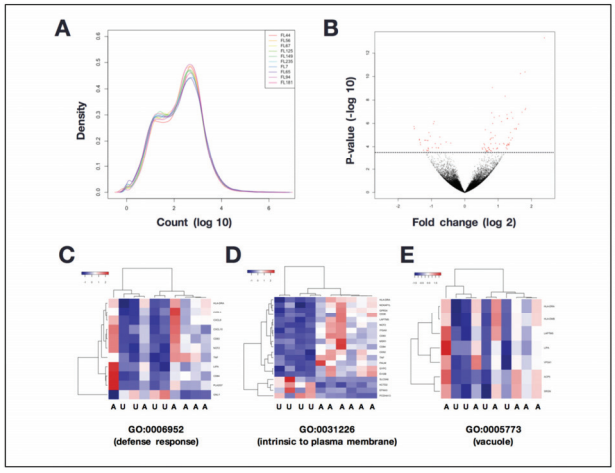

Figure 2. RNA-seq pilot experiment using 4 healthy and 6 NAFLD tissues. (A) Genome-wide transcription expression distribution demonstrating the 10 samples display similar expression pattern after normalization. (B) Differentially expressed genes are selected by multiple-corrected significant changes between the healthy and NAFLD tissue expressions. (C-E) Expression of significantly enriched gene ontology genes.

PE - 147

Biochemical Changes in Non-alcoholic Fatty Liver Disease (NAFLD): A Study in Nepalese Population

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Aims: The present study was conducted with the aim to assess the biochemical markers in Non alcoholic fatty liver disease (NAFLD) patients in Nepalese population.

Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common liver problem in the western world and is a clinicopathologic entity increasingly recognized as a major health burden in developed countries. Different laboratory tests are extremely useful in achieving a better understanding of diseases, and thereby, allow making decision for better management. The examination of different biochemical parameters usually provides excellent clues to the cause of the disease.

Methods: The biochemical parameters were investigated in 75 NAFLD patients, and 70 normal participants. The diagnosis of hepatic steatosis was established by abdominal ultrasound examination. All patients diagnosed as NAFLD were investigated for biochemical parameters and see the relationship between NAFLD and control was studied.

Results: The findings of all biochemical parameters were raised in NAFLD patients in comparison with non-fatty liver control group and the differences were found to be statistically (P value less than 0.005) significant.

Conclusions: NAFLD is associated with changes in biochemical parameters in cases of NAFLD. Its early detection will help in modifying the disease course, delaying complications and will also play a major role in preventive cardiology.

Keywords: Nonalcoholic fatty liver disease (NAFLD), Lipid profile, Liver function test (LFT), Biomarker

PE - 148

Waist Circumference, Not Body Mass Index, Is Associated with Increased Gamma-glutamyltranspeptidase in Type 2 Diabetes Mellitus

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Aims: Serum gamma-glutamyltranspeptidase (GGT), a marker of liver injury, alcohol consumption, and oxidative stress, has been shown to be associated with obesity and diabetes mellitus. Obese individuals with higher GGT are associated with complications in type 2 diabetic patients. There is evidence that waist circumference (WC) measured obesity more accurately than body mass index (BMI). In the present study, we aimed to evaluate association of GGT with WC and BMI in diabetic subjects.

Methods: The study subjects were 105 type 2 diabetic patients (39 men and 66 women), who attended outpatient department of Nepal Medical College Teaching Hospital, Kathmandu, Nepal. The patients with the history of alcohol intake and liver disease were excluded from the study. Anthropometric measurement was taken and venous blood was collected for biochemical analysis. Statistical analysis was done using SPSS 16.0. The p-values less than 0.05 were considered as significant.

Results: The serum GGT levels were positively correlated with blood sugar levels in diabetic subjects. Similarly, GGT levels were positively associated with WC ($r=0.269$, $p<0.05$) in women diabetic patients. However, no such correlation was observed in men diabetic subjects ($r=0.14$). Also, there was no correlation between serum GGT levels and BMI ($r=0.03$), suggesting that regional fat distribution in type 2 diabetes is associated with the increased levels of serum GGT.

Conclusions: In conclusion, WC, not the BMI, is correlated with serum GGT levels in women with type 2 diabetics. Hence, it is important to evaluate central obesity and GGT in patients with diabetes mellitus.

Keywords: Gamma-glutamyltranspeptidase, Waist circumference, Body mass index, Diabetes mellitus

PE - 149

Association of Serum Aminotransferases with High Density Lipoprotein Cholesterol (HDL-C) in Diabetic Patients

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Aims: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are commonly used markers of liver-disorders. Non-alcoholic fatty liver disease (NAFLD) is associated with lipid abnormalities and type 2 Diabetes. Previous studies have suggested elevation in levels of ALT and AST which may serve as markers for NAFLD. However, correlation of liver enzymes and lipid profile has not been well established. Hence, current study was performed to observe the association between aminotransferases and HDL-C in type-2 diabetic patients.

Methods: The study was carried out in Department of Pathology, Nepal Medical College and Teaching Hospital, Kathmandu, Nepal. A total of 103 type 2 diabetic patients, 41 males (mean age: 55.9±13.4) and 62 females (mean age: 49.9±10.6) were included in this study. Patient's anthropometric measurements were performed before collecting the fasting blood for aminotransferases and lipid profile analysis. The results were shown as mean ± SD. P-values less than 0.05 were considered as statistically significant.

Results: In the present study, serum ALT and AST levels were correlated with fasting HDL ($r= -0.419$, $P < 0.05$ and $r= -0.354$, $P < 0.05$ respectively) in women with type 2 diabetes. However, there was no such correlation among these parameters in men diabetic patients. Furthermore, there was no correlation between aminotransferase and fasting TC, TG and LDL levels.

Conclusions: This finding suggests the correlation between aminotransferase and FHDL in diabetic patients. Hence, measurement of aminotransferase and lipid profile has clinical significance in diabetic patients.

Keywords: Diabetes mellitus, Transaminases, Non-alcoholic fatty liver disease, High-density lipoprotein cholesterol

NAFLD, Clinical

PE - 150

Association of Consumption Level of Simple Sugar and Aspartate and Alanine Aminotransferase: A Cross Sectional Observational Study

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Aims: Simple sugar is spotlighted as an important causative factor of diabetes, hypertension, and other metabolic disease. But the rela-

tion between consumption of simple sugar/fructose and non-alcoholic fatty liver disease (NAFLD) was inconclusive in recent two systematic reviews. So, we study the association of consumption level of simple sugar with aminotransferase activity and fatty liver in Korean.

Methods: Four hundred two subjects were enrolled this study from health promotion center. 119 subjects were diagnosed by NAFLD, and 282 subjects were control. All NAFLD patients were diagnosed by ultrasonography within 3 months, alcohol consumption below 140 g/week (male), 70 g/week (female). Who have diabetes, viral hepatitis, other liver disease or metabolic disorders are excluded. Amount of simple sugar intake was assessed by validated questionnaire from Korea Food and Drug Administration.

Results: Total simple sugar slightly high, but not significant between sonographic fatty liver and control group in men (43.63 ± 25.92 vs. 41.73 ± 30.89, p>0.05) and women (46.45 ± 28.93 vs. 42.30 ± 29.42, p>0.05). When the amount of simple sugar divided three groups and adjusted with age and body mass index, lower one third sugar intake group decreased risk of abnormal liver function up to 96% in men (p for trend = 0.02). And lower one third sugar intake group decreased risk of abnormal liver function up to 65% in women (p for trend = 0.004). Middle one third intake group decreased risk of abnormal liver function up to 53%, 64% in men and women respectively.(p for trend = 0.002, 0.004 respectively). But amount of simple intake did not show any correlation with prevalence of NAFLD. Only amount of carbohydrate showed positive correlation with prevalence of NAFLD in men and women.

Conclusions: Prevalence of abnormal ALT level was higher in high simple sugar intake group compare to low simple sugar group. But there is no association of the simple sugar and prevalence of NAFLD.

Keywords: Simple sugar, Asparate aminotransferase, Alanine aminotransferase, NAFLD

PE - 151

Cholesterol-lowering Agents Decreased NAS Score without Intrahepatic Fat Improvement in Patients with Non-alcoholic Fatty Liver Disease: Systematic Review with Meta-analysis

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Aims: A number of clinical trials reported diverse effects of cholesterol-lowering agents in nonalcoholic fatty liver disease (NAFLD) patients. We, therefore, assessed the changes in non-alcoholic steatohepatitis activity score (NAS) and intrahepatic fat contents after treatment with cholesterol lowering agents in NAFLD patients by performing a meta-analysis.

Methods: The Cochrane library, the MEDLINE, and the EMBASE databases were searched until June 2015, without any language restrictions, for randomized controlled trials (RCTs) and non-randomized studies (NRSs); additional references were obtained from reviewed articles. The quality of evidence was assessed using the grading of

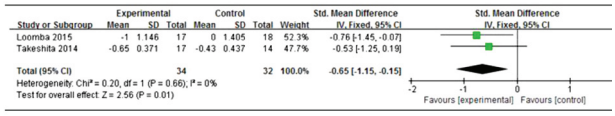

Table 1. Main Characteristics of Included Studies

Study		Loomba_2015[9]	Nelson_2009[5]	Takeshita_2014[7]	Chan_2010[14]	Ekstedt_2007[12]	Kiyici_2003[10]
Location		USA	USA	Japan	Australia	Sweden	Turkey
Ethnicity		White	White, Hispanic, African	Asian	White	White	NA
Study Design		RCT	RCT	RCT	NRS	NRS	NRS
Sample Size	Intervention	25	10	17	15	17	27
	Control	25	6	15	10	51	17
Gender	Male	19	11	20	15	48	24
	Female	31	5	12	10	20	20
Age	Intervention (year)	49±14.9	52.6±8.6	50.4±2.9	57±8	48.7±9.1	43.7±1.8
	Control (year)	49.5±13.7	52.5±13.0	55.5±3.0	57±8	46.3±11.8	50.2±1.4
Baseline	Intervention (mg/dl)	EZE 180	Statin 231	EZE 199	EZE 224.2	Statin 264	Statin 240
Cholesterol	Control (mg/dl)	Placebo 170	Placebo 210	Placebo 199	Placebo 224	Placebo 230	UDCA 170
Inclusion criteria		NASH	NASH	NAFLD	Central obesity	NAFLD	NASH
Study Modality		Biopsy and MRS	Biopsy	Biopsy	MRS	Biopsy	CT
Treatment duration		6 months	12 months	6 months	22 weeks	6.1 years	6 months
Diabetes		28%	NA	eNA	Exclusion	80%	20%
Baseline BMI (kg/m2)		BMI 33-34	BMI 34-37	BMI 28-31	BMI 32-33	BMI 27-30	BMI 29
Baseline BWt.(kg)		BWt 92-94		BWt 73-74	BWt 94-100		
BWt. Change		(-)	(-)	(-)	6-7kg loss	(-)	(-)

Mean±standard deviation is presented for normally distributed variables.
Abbreviations: RCT, randomized controlled trials; NRS, non-randomized studies; EZE, ezetimibe; BMI, body mass index; BWt, body weight; NA, not available. *Paired liver biopsy patents only.

recommendations assessment, development and evaluation guidelines.

Results: Three RCTs and three NRSs (235 participants) met the inclusion criteria for this updated systematic review. Liver biopsy was performed in three RCTs, but only the two studies reported NAS. Ezetimibe showed decreased NAS (Pooled RR: -0.65, 95% CI: -1.15 ~ -0.015). The intrahepatic fat contents were not decreased in RCTs, while they were decreased in NRSs. The baseline cholesterol level in all three RCTs was lower than the three NRSs (191mg/dl vs. 227.5mg/dl). The pre-planned secondary outcomes of AST, ALT, Glucose, HbA1c analysis did not show significant difference after treatment with cholesterol lowering agents.

Conclusions: Ezetemibe decreased NAS score without improving intrahepatic fat contents.

Keywords: NAFLD, NASH, Ezetimibe, Statin

PE - 152

Development of a Novel Simple Model for Predicting NASH in a Huge Biopsy-proven NAFLD Cohort

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Aims: Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH) which may progress to cirrhosis and hepatocellular carcinoma. We aimed to characterize a huge biopsy-proven NAFLD cohort in Korea and to investigate the association between serum biochemical markers and anthropometric measurements and biopsy-proven NASH.

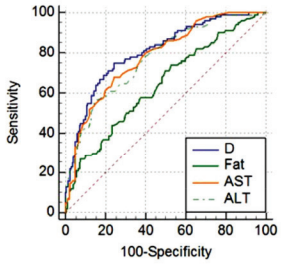
Methods: A total of 315 biopsy-proven NAFLD patients were included in this prospective cross-sectional analysis. The anthropometric data including total body fat mass and total muscle mass were measured using bioelectrical impedance analysis. To find the independent factors for NASH development, logistic regression analysis was conducted. Discriminant function analysis was performed stepwise to test the ability of independent variables in predicting NASH. The area under the receiver operating characteristic (AUROC) curve was used to determine the optimal cut-off point, sensitivity, and specificity of discriminant function formula for detecting NASH (D).

Results: In multivariate logistic regression analysis, independent pre-

Table 1. Univariate analysis and Multivariate analysis to identify independent variables related to prevalence of NASH

	Univariate Analysis			Multivariate Analysis		
Characteristics	OR	95% CI	p value	OR	95% CI	p value
Age(yr)	0.982	0.967-0.998	0.023	0.996	0.970-1.022	0.757
Sex	1.315	0.825-2.097	0.249	0.911	0.450-1.844	0.795
BMI(kg/m^2)	1.102	1.030-1.179	0.005	0.911	0.764-1.086	0.299
Skeletal muscle mass(kg)	1.006	0.971-1.043	0.731			
Body fat mass(kg)	1.07	1.034-1.107	<0.0001	1.1	1.007-1.201	0.035
DM	0.659	0.403-1.078	0.097			
HT	1.231	0.765-1.981	0.391			
MS	1.45	0.892-2.357	0.134			
AST(units/L)	1.033	1.021-1.044	<0.0001	1.021	1.002-1.039	0.029
ALT(units/L)	1.022	1.015-1.029	<0.0001	1.013	1.002-1.039	0.021
γGT(units/L)	1.00	0.998-1.002	0.999			
Chol(mg/dL)	1.005	0.999-1.011	0.12			
Albumin(g/dL)	2.405	1.076-5.375	0.032	2.279	0.775-6.702	0.135
INR	1.049	0.068-1.618	0.973			
Platelet count(k/uL)	1.002	0.999-1.006	0.187			
Adipose tissue IR	1.065	1.083-1.103	<0.0001	1.021	0.981-1.063	0.316
Use of statin	0.607	0.365-1.011	0.055			
Use of antiHT	1.114	0.692-1.792	0.656			

BMI: Body mass index, DM=Diabetes mellitus, HT=Hypertension, MS=Metabolic syndrome, AST: Aspartate transaminase, ALT: Alanine transaminase, γGT: Gamma glutamyl transpeptidase, Chol: Cholesterol, INR: International normalized ratio, Adipose tissue IR: Adipose tissue insulin resistance



p value	D	Fat	AST	ALT
D		<0.001	0.196	0.086
Fat	<0.001		0.001	0.002
AST	0.196	0.001		0.709
ALT	0.086	0.002	0.709	

D=-2.518640+0.048152*Fat+0.013731*AST+0.013297*ALT

	NASH presence vs. absence			
	D	Fat	AST	ALT
Cutoff value	-0.0605	21.3	43	67
Sensitivity (%)	72.12	71.00	66.98	54.72
Specificity (%)	76.44	50.25	73.68	84.69
AUROC	0.787	0.640	0.770	0.756
95% Confidence interval	0.738-0.831	0.583-0.695	0.719-0.815	0.705-0.803
p value	<0.001	0.639	<0.001	<0.001

dictors of biopsy-proven NASH were body fat mass (OR, 1.1; 95% CI, 1.007-1.201; p=0.035), aspartate transaminase (AST) (OR, 1.021; 95% CI, 1.002-1.039; p=0.029), and alanine transaminase (ALT) (OR, 1.013; 95% CI, 1.002-1.039; p= 0.021). D was derived as follows: −2.518640 + 0.048152×Fat + 0.013731×AST + 0.013297×ALT. The AUROC for value of D was 0.787 (optimal cut-off, -0.0605; sensitivity, 72.12%; specificity, 76.44%) for predicting biopsy-proven NASH. The predictive performance of D was superior to that of each independent predictor (body fat mass, 0.640; AST, 0.770; and ALT, 0.756).

Conclusions: The established D based on body fat mass, AST, and ALT is able to accurately predict the presence of NASH, which may obviate unnecessary liver biopsy in patients with NAFLD. Therefore, additional prospective large-scale studies are warranted to validate this simple novel model (D) for predicting NASH.

Keywords: NAFLD, NASH, Total body fat mass, AST, ALT

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The Application of the Fatty Liver Inhibition of Progression (FLIP) Algorithm and Steatosis, Activity, and Fibrosis (SAF) Score in Korean Patients with Nonalcoholic Fatty Liver Disease

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Aims: Biopsy is still the gold standard for the diagnosis of nonalcoholic steatohepatitis (NASH) but the definition may vary in evaluation of biopsies for clinical trials. Recently, a scoring system (steatosis, activity, fibrosis[SAF]) allowing the use of an algorithm (fatty liver inhibition of progression [FLIP]) reported for the classification of liver injury in morbid obesity. We evaluated the application of SAF score and FLIP algorithm in Korean patients with nonalcoholic fatty liver disease (NAFLD).

Methods: We analyzed the 126 patients with biopsy-proven NAFLD in 5 centers in Korea from Aug, 2008 to April, 2016.

Results: In total study populations, 56 patients (44.4 %) were diagnosed to NASH, 70 (55.6%) as NAFLD including 60 patients of a gray zone (NAS 3-4) according to NAS scoring system. Based FLIP algorithms, 72 patients (57.1 %) were categorized as NASH, 54 (42.9 %) as NAFLD. 21 patients (35%) in gray zone (NAS 3-4) and 5 patients (NAS ≥5) were categorized as NASH and steatosis, respectively. The activity score (ballooning+ lobular inflammation) enabled discriminating NASH. All patients with NASH had A ≥3, whereas 3 patients (5.2%) with A2 had NASH. Especially, the presence of ballooning in activity score was the significant factor to discriminate NASH and steatosis. This activity score was also closely correlated with both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and Fragmented cytokeratin-18, respectively (P=0.000, 0.023, 0.006 respectively). Fibrosis grade by SAF score was significantly correlated with NAFLD fibrosis score and fibroscan (P=0.026, 0.000, respectively).

Conclusions: The FLIP algorithm and SAF score system in the NAFLD may provide the favorable tools in Korean patients. Among the SAF score, the ballooning of hepatocyte may be an important factor to discriminate NASH and NAFLD, although it is one of the major limitations of liver biopsy.

Keywords: Nonalcoholic steatohepatitis, SAF, FLIP

Other Surgical Issues

PE - 154

Surgical Treatment of Liver Alveococcosis

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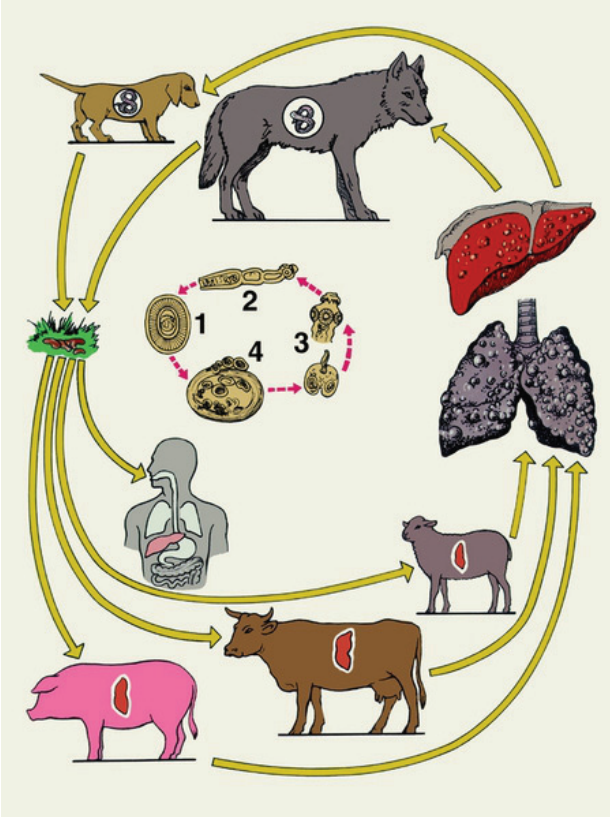
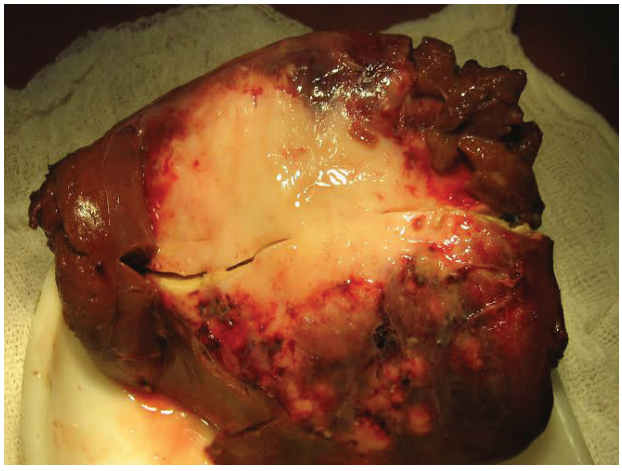
Aims: Alveococcosis - a parasitic disease caused by echinococcus multilocularis larvae and proceeding with the formation of the primary liver tumor. Alveococcosis complications may include festering parasitic tumor, a rupture in the formation of peritoneal or pleural cavity,





jaundice, portal hypertension, alveococcus metastasis into brain and lungs. In terms of surgical tactics at liver alveococcosis, the most difficult issues are the choice of the optimal variant of surgical intervention and liver resection volume.

Methods: Experience of observation over 36 patients with alveococcosis within 2 years is the basis for this presentation. Radical liver resection is performed on 30 patients, the other 6 patients had the unresectable alveococcosis volume. After radical liver resection alveococcosis relapse was observed on 1 patient. At the impossibility to execute radical surgery, resection - bone removal and palliative interventions remain the only surgery options.

Results: During intrasurgical audit, mainly right lobe impairment has been revealed on 28 (93,3%) patients, 5 (17,8%) of them had parasitic knots crossed to segments of the left lobe of a liver. 2 (6,7%) patients had tumor generally localized separately in the left lobe of a liver without spreading to the adjacent organs. Germination in the adjacent organs was observed at 2 (7,1%) patients in the 1st group (to a diaphragm). In the same group one patient had lymph nodes of colon impaired, and 2 (7,1%) patients had the remote metastasises of abdominal cavity settled down in retroperitoneum (in the lower hollow vein and a tail of a pancreas).

Often, parasitic impairment of an alveococcosis is massive which in some observations demands non-standard approach to treatment of such patients. Separate attention should be given to some clinical observations. Two-stage surgical treatment carried out for 25 years old patient. First, right-sided hemihepatectomia was performed (first phase), then, 12 months later atypical resection of segments II and III was performed (the second phase). In order to achieve a radical intervention for a 42 year-old patient, the resection of the V-VI liver segments, an atypical resection of the VII segment and a bisegmentectomy of the II-III segments were augmented with a radio-frequency ablation of two small (diameter to 1 cm) centers in the VII liver segment.

During 2 years of treatment she had been receiving chemotherapy with albendazole, in 2 years after surgery CT of an abdominal cavity in the VII segment will reveal postablation lesions; no signs of disease recurrence present.

Conclusions: Thus, alveococcosis remains surgicai- dependent disease. Radical resection during alveococcosis is abie to heal completely majoriti of patients and brings good results in the further perspective. I wonder alveococcosis liver surgery because I was ill alveococcosis liver and underwent surgical treatment. Now I'm alive and well.

Keywords: Alveococcosis, Liver, Resection, Chemotherapy

PE - 155

The Predicting Factors for Mortality after Hip Surgery in Cirrhotic Patients

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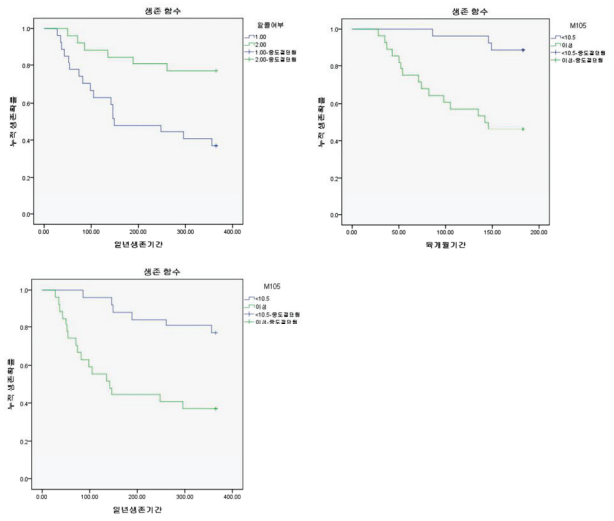
Aims: Cirrhosis increases the risk of osteoporosis and fracture. However, there are sparse data about outcome of hip fracture in cirrhotic patients. We investigated the predictors for mortality in cirrhotic patients with hip fracture underwent surgery.

Methods: A total of 56 cirrhotic patients with hip surgery were retrospectively enrolled between 2006 and 2015. The cause of cirrhosis, Child-Turcotte-Pugh (CTP), model for end stage liver disease (MELD) score, operation record, peri-operative complication, hospital length of stay, in-hospital, 6-month and 1-year mortality after hip fracture were investigated.



Results: Six patients (11%) died after hip surgery. Serum platelet, CTP and MELD score at the time of admission were associated with in-hospital mortality. On multivariate analysis, CTP and MELD score were independent factors predicting in-hospital mortality (CTP score: relative risk, 3.219; 95% CI, 1.378 to 7.520; P=0.007, MELD score: relative risk, 3.772; 95% CI, 1.038 to 13.707; P=0.044). The AUROC of MELD score was 0.925 (P=0.001; 95% CI: 0.832-1.00). MELD score ≥ 12.5 was associated with in-hospital mortality. (sensitivity 100%, specificity 76%). Six months and one year after surgery, 18 patients (32.1%) and 25 patients (44.6%) died, respectively. MELD score and the cause of cirrhosis (alcohol) were associated with 6-month and 1-year mortality. On multivariate analysis, MELD score was independent factor predicting 6-month mortality (relative risk, 1.158; 95% CI, 1.009 to 1.329; P=0.037) and the cause of cirrhosis (alcohol) was the only independent factor predicting 1-year mortality (relative risk, 4.222; 95% CI, 1.197 to 14.896; P=0.025).

Conclusions: CTP and MELD score were important predictors for in-hospital mortality after hip surgery in cirrhotic patients. Although the hip surgery was performed successfully, long term prognosis was poor especially in alcoholic cirrhotic patients.

Keywords: Hip fracture, Liver cirrhosis, Mortality

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Results of Involving of "Roncoleukin" in Autologous Erythrocyte Shells in Patients with Surgical Sepsis (In Vitro Study)

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Aim: To improve the results of complex surgical treatment of patients with sepsis, by applying of established transport systems of targeted delivery of "Roncoleukin®" included in autologous erythrocyte shells

Methods: To achieve this goal we have conducted the first phase of research - the inclusion of "Roncoleukin®" in autologous erythrocyte shells in patients with surgical sepsis. 12 patients of either sex with a diagnosis of the surgical sepsis, 5 ml of blood from the cubital vein was taken. In sterile conditions, the blood was distributed in four tubes containing heparin. "Roncoleukin®". Units included in the shells of erythrocyte on hypotonic hemolysis method (Pf. Zh.Sh.Zhumadilova et al.).

Results: In vitro laboratory experiments have shown that content of "Roncoleukin®" in suspension was equal to an average of 2535 ± 119,8 pg/ml, in supernatant - 2790 ± 95,8 pg/ml. There were no significant difference between contain of "Roncoleukin®" in suspension and supernatant. Content of "Roncoleukin®" in the supernatant was only 1.1 times higher than its content in the suspension, which was not statistically significant (p>0.05). The content of "Roncoleukin®" in hemolysate averaged 16040 ± 838,3 pg/ml, which is higher than its content in suspension and supernatant 6.3 and 5.7 times, respectively. The difference of index of "Roncoleukin®"in hemolysate and suspension, as well as in the hemolysate, and supernatant is statistically significant (p <0.001).

Conclusion: This data demonstrate the possibility of including of "Roncoleukin®" in erythrocyte shells. Injection of erythrocyte pharmacocytes with "Roncoleukin®" can result high concentration of drug in target organs, given its high content in erythrocyte shadows that will improve the results of treatment of patients with surgical sepsis.

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Surgery for Metachronous Liver Metastases from Stomach Cancer

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Aims: The role of surgical therapy in patients with metachronous liver metastases from stomach cancer is still controversial. In this study, we evaluated surgical outcome of liver metastases in patients with stomach cancer by comparing chemotherapy.

Methods: From January 1997 to December 2010, 180 medical records of the patients were retrospectively reviewed, who were diagnosed metachronous metastasis that was confined to liver after radical gas-

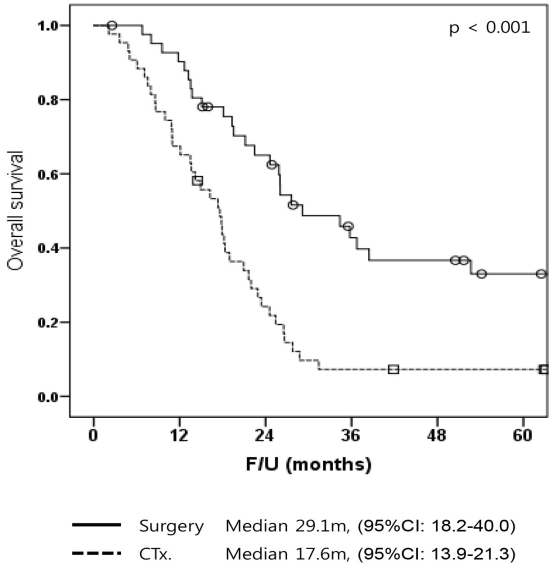

Table . Clinicopathologic characteristics according to treatment modality for liver metastasis

	Surgery (N=33)	Chemotherapy (N=40)	p value
Gender (M : F)	26 : 7 (3.7 : 1)	35 : 5 (7.0 : 1)	0.357
Age (Stomach cancer, yr)	58.6 ± 9.6	61.2 ± 10.1	0.272
Age (Liver metastasis, yr)	59.9 ± 9.7	62.6 ± 10.3	0.260
DFS (m)	14.5 ± 13.6	15.3 ± 18.8	0.835
Tumor location			0.947
Upper	6 (18.2%)	7 (17.5%)	
Middle	7 (21.2%)	10 (25.0%)	
Lower	20 (60.6%)	23 (57.5%)	
Stomach operation			0.630
Subtotal	22 (66.7%)	24 (60.0%)	
Total	11 (33.3%)	16 (40.0%)	
Stomach tumor size	4.3 ± 1.6	5.3 ± 2.7	0.060
TNM stage			0.273
I	2 (6.0%)	0 (0.0%)	
II	15 (45.5%)	16 (40.0%)	
III	16 (48.5%)	24 (60.0%)	
Differentiation			0.186
Differentiated	22 (66.7%)	22 (55.0%)	
Undifferentiated	8 (24.2%)	17 (42.5%)	
Others	3 (9.1%)	1 (2.5%)	
LVI (N=62)	18 (60.0%)	25 (78.1%)	0.170
PNI (N=51)	11 (40.7%)	13 (54.2%)	0.406
Recur size	2.5 ± 1.1	2.8 ± 2.4	0.386
Recur number			<0.999
1	23 (69.7%)	27 (67.5%)	
2-3	10 (30.1%)	13 (32.5%)	

trectomy for stomach cancer. Among them, multiple liver metastatic (> 3) patients and untreated patients were excluded. Consequently, 85 patients were enrolled. In the patients, overall survival (OS) was compared between patients who were performed liver resection and patients who were performed chemotherapy.

Results: 42 patients were performed liver resection (Surgery group) and 43 patients were performed chemotherapy (Chemotherapy group). Disease free survival without liver metastasis was 14.9 months and 61 (71.8%) patients were revealed single liver metastasis. There were no significant differences in age, pathologic status of stomach cancer (e.g. location, size, stage, differentiation, lymphovascular invasion and perineural invasion) except tumor size (Surgery vs. Chemotherapy: 4.0±1.6cm vs. 5.2±2.7cm, p=0.013) There were also no significant differences in recurred tumor size and numbers. In survival analysis, the surgery group was superior in OS to the chemotherapy group. (Surgery vs. Chemotherapy: 29.1m (95%CI: 18.2-40.0) vs. 17.6m (95%CI: 13.9-21.3), p<0.001)

Conclusions: Curative and also palliative surgery of metachronous liver metastases from stomach cancer may improve patients' survival.

Keywords: Stomach cancer, Liver metastases, Surgery, Outcome

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Damage Control Measures In Major Liver Trauma

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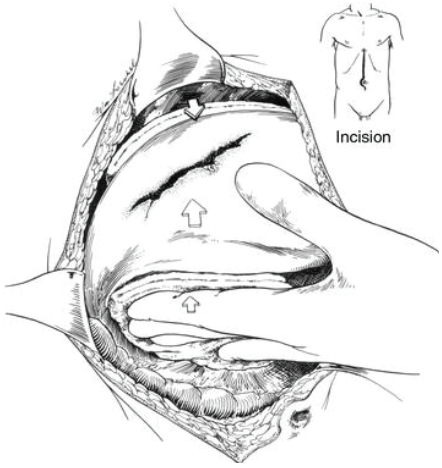
Aims: Main aim of the study was Do minimum and get maximum. Despite the fact that treatment of liver injuries has dramatically evolved, severe liver traumas in polytraumatic patients still have a significant morbidity and mortality1. Massive trauma and abdominal



catastrophes carry high morbidity and mortality. In addition to the primary pathologic process, a secondary systemic injury, characterized by inflammatory mediator release, contributes to subsequent cellular, end-organ, and systemic dysfunction. These processes, in conjunction with large-volume resuscitations and tissue hypoperfusion, lead to acidosis, coagulopathy, and hypothermia2. Here we present a case with Grade 4 Liver Trauma injury.

Methods: A 35 years old man admitted in emergency with history of blunt trauma abdomen. He had features of shock and initially resuscitation was not successful. On exploration, apart from gut injury there was huge laceration of liver involving segment 6, 7 and 8. Patient was resuscitated twice during surgery and later on we decided to take damage control measures. Perihepatic packing was done around liver, abdomen cavity was not closed and a plastic bag was applied. Coagulopathy was corrected, steroids were given, acidosis was also corrected. After 48 hours packing was removed and liver laceration was repaired.

Results: After first surgery patient was made stable hemodynamically. To avoid abdomen compartment, cavity was left open. On secondary visit Patient was stable and easy to mange. He was then discharged from hospital after one week.

Conclusions: In liver Trauma patients of grade 4 or above or associated with other injuries we should always think of take some measure of damage control instead of prolonging the duration of surgery. By doing little we can get the maximum as per the emergency principle. This case was unique for us as it was first case operated in this center where numbers of cases are very less.

Keywords: Trauma, Damage control

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Laparoscopic Bile Duct Exploration with Glissonian Approach and Individual Dissection (Laparoscopic Glissonian Approach : Bile Duct Exploration Using Combination of Glissonian Approach and Individual Dissection)

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Purpose: Laparoscopic Glossonian approach is very useful method not only in open hepatectomy but also in laparoscopic hepatectomy. Laparoscopic Glissonian approach followed by individual dissection makes it easy and safe for individualization of portal triad. Moreover, in the case of impacted bile duct stone in the hilar area, it makes easy bile duct exploration without blood loss.
Method: Laparoscopic Glissonian approach and extracorporeal control of Glissonian pedicle make it easy and safe dissection of parenchyma and pedicle control. Hepatectomy including bile duct exploration by using combination of Glissonian approach followed by individual dissection could help bile duct exploration easy without bleeding. If IHD stone was located in the main bifurcation, bile duct exploration should be required. Glissonian approach made identification of left pedicle more easy. After isolation of left pedicle, individual dissection of hepatic artery and left portal vein was easy and safe. After dissection of liver parenchyma using Glissonian approach, bile duct exploration with ligation of left hepatic artery and portal vein performed.
Result: This combination method has the advantages of Glissonian approach such as, short operation time and easy approach of hilum. Moreover, it makes bloodless and safe bile duct exploration in hilar type IHD stone.
Conclusion: Combination of Glissonian approach and individual dissection is useful method in laparoscopic liver resection requiring bile duct exploration.
We report the case of a 59-year-old female patient with Left IHD stone located from bifurcation to peripheral area in the left hepatic lobe. Laparoscopic left hepatectomy without bile duct exploration could result in remnant stone in bifurcation sometimes. Left hepatectomy including bile duct exploration by using combination of Glissonian approach and individual dissection could help bile duct exploration easy without bleeding. If IHD stone was located in the main bifurcation, bile duct exploration should be required. Glissonian approach made identification of left pedicle more easy. After isolation of left pedicle, individual dissection of left hepatic artery and left portal vein was easy and safe. After dissection of liver parenchyma using Glissonian approach, bile duct exploration with ligation of left hepatic artery and portal vein performed. The advantage of combination method is easy and safe hepatectomy and bile duct exploration could be achieved.

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Robotic ALPPS in a Patient with Cecal Cancer and Multiple Liver Metastasis (with Video)

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Purpose: The Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) procedure is a new innovative surgical strategy aiming to potentially overcome the liver failure, thus permitting extended hepatectomy.
Methods: A 41 year old female with cecal adenocarcinoma with synchronous numerous liver metastases in near all segments (S1, S3, S4, S5, S6, S7 and S8) underwent Avastin and FOLFOX neoadjuvant therapy. S2 was free from metastasis. One small metastastic lesion was detected in S3 and S1, respectively. To increase a resectability in this patient, we performed ALPPS using daVinci Surgical System.
Results: In the first operation, robotic right hemicolectomy was first performed. After that, wedge resection of small metastatic lesions in S3 and S1 was done. The parechymal was transected along the right side of the umbilical ligament. The middle hepatic vein was completely isolated and encircled with a vessel loop. After the parenchymal transection was completed, the hilum started to be dissected. The right hepatic artery was isolated and encircled with a vessel loop. The right portal vein was dissected and sectioned with hem-o-lock clips. To prevent adhesion, anti-adhesive solution was irrigated within the surgical field. The second stage was performed totally robotic on 11th postoperative days. Postoperative adhesion was dissected. After the right liver was mobilized, the right hepatic artery was sectioned. The remaining liver parenchyma was completed transected. Middle hepatic vein and right hepatic vein were ligated with Endo-GIA. Total operation time was 332 minutes and estimated blood loss was 70ml. The patient recovered well and was discharged 20 days after the second stage.
Conclusion: Robotic ALPPS procedure can be a safe and feasible technique in experienced centers with advanced robotic skills.

Others

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Estimation of Willingness to Pay for a Quality-adjusted Life Year on a Cure

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Aims: The cost-effectiveness of a medicine is an important factor in its reimbursement with one of the most important criteria being the social willingness to pay (WTP). Recently, with the introduction of the curative medicines, the need to understand the WTP of these treatments has appeared. This study aimed to estimate WTP per quality-adjusted life year (QALY) for a cure for Korean general population.
Methods: Five hundreds and seven subjects, proportionally assigned by sex, age, and region, participated at the face-to-face interview. The contingent valuation survey was conducted for 4 EQ-5D scenarios with different health status. We assumed a treatment which moved from the health status of each scenario to perfect health. WTP for one year of the treatment was derived using double-bounded format followed by open-ended answer. The post-treatment effect continued for a fixed period (5 years, 10 years, and lifetime) in cure scenario. In non-cure scenario, the effect instantly stopped when treatment terminated. For identifying factors influencing WTP, the multi-level analysis was performed.
Results: WTP per QALY for non-cure scenario was KRW 15 million/QALY. The cure scenario for 5 years, 10 years, and lifetime resulted in KRW 22 million/QALY, KRW 27 million/QALY, and KRW 35 million/QALY, respectively. Thus, the increased rate of WTP in cure scenario for 5 years, 10 years, and lifetime based on the non-cure were

1.4, 1.8, and 2.3 times higher, respectively. In all scenarios, the statistically significant factors affecting WTP per QALY were high education, high house income, and health care provider.

Conclusions: Through this study, we identified that WTP for cure treatment was substantially higher than that of non-cure. This higher WTP should be considered for decision-making of curative treatments in the future.

Keywords: Willingness to pay, Cure, QALY, WTP

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The Degree of Liver Fibrosis Assessed Using Transient Elastography Independently Correlates with the Risk of Stroke: A Case-control Study

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Aims: Transient elastography (TE) assess the degree of liver fibrosis and steatosis. The degree of liver fibrosis was associated with the presence and burden of cerebral microbleeds in healthy, asymptomatic participants. We investigated the correlation between the degree of liver fibrosis, as assessed using TE, and the risk of stroke.

Methods: Patients who were admitted due to the management of stroke and received TE examination from April 2013 to August 2014 and subjects who underwent a medical health check-up including TE during the same period were recruited. Significant fibrosis was defined as a liver stiffness (LS) value of ≥8 kPa and hepatic steatosis was defined as a controlled attenuation parameter (CAP) of ≥250 dB/m. Subjects with inappropriate TE results and alcoholic/ chronic viral liver diseases were excluded. Further, we conducted propensity score matching to reduce the potential effects of selection bias and confounding factors.

Results: A total of 295 patients with stroke and 2,936 subjects with health check-up were analyzed. The mean age and the proportion of hypertension, diabetes, hypercholesterolemia, chronic kidney disease, and metabolic syndrome were significantly higher in patients with stroke than those of subjects with health check-up (all P<0.05). The mean LS value (5.6 kPa, vs. 4.2 kPa) and the proportion of significant fibrosis (9.2% vs. 2.7%) were significantly higher in patients with stroke than those of subjects with health check-up (all P<0.05), whereas the mean CAP value and the proportion of hepatic steatosis were statistically similar between two groups (all P>0.05). When fibrotic burden was assessed using TE, it was significantly higher in patients with stroke than that of subjects with health check-up, regardless of body mass index (BMI) (mean 5.3 kPa vs. 3.9 kPa in BMI<25 kg/m^2 and 6.3 kPa vs. 4.7 kPa in BMI ≥25 kg/m^2), CAP value (mean 5.3 kPa vs. 3.9 kPa in CAP<250 dB/m and 6.3 kPa vs. 4.7 kPa in CAP≥250 dB/m), and metabolic syndrome (mean 5.3 kPa vs. 4.1 kPa in the absence of metabolic syndrome and 5.9 kPa vs. 5.0 kPa in the presence of metabolic syndrome) (all P<0.05). As a continuous variable, unadjusted odd ratio (OR) of LS value for stroke was 1.161 and adjusted ORs were calculated as between 1.132 to 1.213 according to varying multivariate models. As a categorical variable, unadjusted OR of significant fibrosis was 4.388 and adjusted ORs were calculated as between 3.474 to 6.397 according to varying multivariate models. In a propensity matched analysis using 1:1 ratio (n=197 for each group), LS value was independently associated with the risk of stroke (OR of 1.080 as a continuous variable and 8.488 as a categorical variable) (all P<0.001).

Conclusions: In our case-control study, we found that the degree of liver fibrosis, as assessed using TE, was significantly associated with the risk of stroke. Further studies investigating the dynamic link between these two disease entities are required.

Keywords: Transient elastography, Stroke, Liver fibrosis, Fibroscan

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Association Liver Enzymes with Blood Pressure in Diabetic Patients

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Aims: Gamma-glutamytransferase (GGT) is routinely used laboratory investigation for liver damage and alcohol consumption. Serum GGT concentration is determined by body fat content, lipid and glucose levels, alcohol consumption and various medications. Several lines of evidence show that serum GGT is associated with cardiovascular and all-case mortality. It is also a marker of oxidative stress. Although serum GGT is associated with hypertension, the correlation between GGT and blood pressure has not been well established. The aim of the present study was to investigate the association between serum GGT and blood pressure in type 2 diabetic patients (T2DM).

Methods: A total number of 105 patients with T2DM, who attended Nepal Medical College Teaching Hospital, Kathmandu, Nepal, were recruited for the study. There were 39 males (mean age: 56.6±5.2 years) and 66 females (mean age: 49.6±6.3). The patients with history of liver disease and alcohol intake were excluded from the study. After basic anthropometric measurement, fasting venous blood was collected and subjected for the estimation of liver enzymes. All data were expressed as mean± SD. p-values less than 0.05 were considered as statistically significant.

Results: Although serum ALT and AST levels were significantly elevated within the normal range in T2DM compared to control, they are not correlated with systolic blood pressure (SBP) (r= 0.07 and 0.128, respectively) and diastolic blood pressure (DBP) (r= 0.08 and 0.02, respectively) in both men and women. However, serum GGT levels within their normal range were positively correlated with SBP (r=0.4, p<0.01) and DBP (r=0.275, p<0.05) in women. Interestingly, neither of these liver enzymes was correlated with blood pressure among men diabetic patients.

Conclusions: These findings suggest that GGT may be linked with blood pressure balance in women and evaluating the levels of GGT

could help in the monitoring of hypertension in diabetic individuals.
Keywords: Liver enzymes, Biliary tract enzymes, Diabetes mellitus, Hypertension

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Impact of Ledipasvir/Sofosbuvir on the Work Productivity of Chronic Hepatitis C Patients in Asia

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Aims: To estimate the work productivity gains associated with LDV/SOF treatment for CHC in Hong Kong, Singapore, South Korea and Taiwan.
Methods: The model captures anticipated impact of LDV/SOF on productivity loss over a one-year time horizon from a societal perspective for each country. A literature review was performed to identify country-specific inputs and expert advice was solicited to verify key variables. Patients enter the model post-treatment, having achieved SVR12, or not. Absenteeism and presenteeism rates were estimated based on the Work Productivity and Activity Index-Specific Health Problem (WPAI-SHP) data collected from the Phase III ION trials (US participants only) at baseline and at 12 weeks with rates assumed to remain unchanged from baseline for patients not achieving SVR. Sensitivity analyses were performed on key variables.
Results: Total Work productivity loss due to not treating CHC was highest in Taiwan at US$349M ($355 per capita) given high prevalence of HCV, followed by US$146M ($358) in Korea, US$17M ($914) in Singapore and US$11M ($351) in Hong Kong. Treatment with LDV/SOF resulted in estimated productivity gains of $138 million, $58.7 million, $6.8 million and $4.5 million in Taiwan, Korea, Singapore and Hong Kong respectively.
Conclusions: CHC imposes a significant indirect economic burden. Our model demonstrates that treatment of HCV GT1 patients with LDV/SOF is likely to result in significant cost savings due to an improvement in presenteeism versus no treatment across 4 Asian countries. This indirect economic gain should be considered when assessing the benefits of treating CHC.
Keywords: LDV/SOF, Work productivity, Chronic hepatitis C, Asia

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Pyloric Gland Adenoma of the Common Bile Duct: A Case Report and Review of Literature

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Aims: A pylori gland adenoma(PGA) is a rare tumor found in the gastrointestinal tract. It is most commonly located in the stomach, but very rarely found in the common bile duct(CBD). In the literature, there are only 4 reported cases of PGA in the CBD and, to our knowledge, this is the first report done in the Philippines.
Methods: We present the case of a 75-year old male who complained of progressive jaundice, pruritus, tea-colored urine and acholic stools for one month.
Results: Bilirubin, AST, ALT and alkaline phosphatase were elevated. Ultrasound showed dilated intrahepatic ducts and CBD. ERCP revealed a 2.3cm dilated bile duct with an irregular filling defect at the distal portion causing the inability to deep cannulate the bile duct. MRI with MRCP demostrated marked intrahepatic and extrahepatic biliary ductal dilatation with CBD measuring 3.5cm and a lobulated intraductal mass that was considered as cholangiocarcinoma. The patient underwent exploratory laparotomy with duodenotomy and ampulectomy and a light to dark brown, fleshy pedunculated mass was excised. Upon histopathological analysis, the mass was consistent with PGA.
Conclusions: The diagnosis of these lesions pose a challenge to clinicians; therefore, it is important to correctly interpret radiologic imaging tests and correlate them with the clinical findings and histopathological results. Although very rare, it should be considered as a differential diagnosis for an obstructive biliary tumor. Due to its high risk malignancy conversion potential, complete surgical resection is recommended for all PGA.
Keywords: Pyloric gland adenoma, Common bile duct mass, Case report

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The Role of Endoscopic Ultrasound in a Tertiary Hospital: Past and Present

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Aims: Endoscopic Ultrasound (EUS) is an emerging diagnostic modality for the GI tract. The aim of this study is to determine the demographic profile, common indications, findings and diagnosis of patients who underwent endoscopic ultrasound Also, another aim of this study is to compare the profile, usual indications and diagnosis of patients who underwent EUS before 2013 and from September 2015 to present.
Methods: This is a retrospective cross-sectional study of all adult patients who underwent endoscopic ultrasound from January 1, 2008 to February 22, 2016. Data were encoded using MS Excel and analysis was done using SPSS.
Results: Among 482 patients who underwent EUS, mean age was 57 with almost equal ratio for males (49.8%) and females (50.2%). Majority of patients had a CT scan (34%) done prior to procedure. Most patients were given sedation with Propofol (36.7%). Majority of patients (68.3%) had an upper EUS. The most common indication

was to do further studies for rectal masses (23.9]. The most common diagnosis was rectal malignancy (20.5). Hepatoma was found in 2.7%. The difference among the past and present groups was found to be statistically significant with the type of sedation (increase in Propofol use) and type of endoscopy (increase in upper EUS) with p value <0.001). For the past group, the top indication was rectal mass (26.2%) while in the present group, the top was pancreatic mass (21.1%). The top diagnosis in the past was rectal malignancy (22.6%) while in the present, it was GIST (17%).

Conclusions: Endoscopic ultrasound has emerged into a highly effective tool in diagnosing and treating gastrointestinal diseases. Being a relatively underutilized tool in our country, there is a need to continue striving for increased utilization to maximize its benefit to our patients.

Keywords: Endoscopic ultrasound, EUS, Retrospective

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High Prevalence of Comorbidities and Contraindicated Medications in HCV Patients in Japan

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Aims: To determine the prevalence of comorbidities and drug-drug interactions (DDIs) in CHC patients in Japan.

Methods: Patients were identified using the ICD10 code for CHC in the Japanese Medical Data Center (MDC) database (04/2008-08/2014). Prescriptions were categorized as either red (contraindicated) or amber (additional monitoring/dose reduction required) for DDI potential with at least one currently licensed direct-acting antiviral (DAA).

Results: 92,294 patients were identified, average age was 68 and 52% male. 82% of patients had one or more comorbidity; the number with 6+ comorbidities increased with age from 2% of patients aged 18-34 to 17% for patients 75+. The most common were hypertension (44%), chronic gastritis (33%) and gastro-oesophageal reflux disease (32%). 74% were treated with amber DDIs and 26% were on red. Polypharmacy increased with age, from 43% for 18-34 to 82% for 75+ (amber) and from 13% to 29% for 18-34 year olds and 75+ respectively (red). Only 8.2% of patients were treated for CHC. Of these, 81% had a potential DDI, increasing from 61% for 18-34 years to 90% for 75+.

Conclusions: We observed significant co-morbidity and co-prescribing with DDI potential in CHC patients in Japan. Few patients received SVR treatment, indicating a large unmet need in Japan. With the treatment shift from interferon to DAA's, more patients may receive treatment. Hence, the high proportion of co-medications contra-indicated to all DAA's vs. only some suggests careful selection of the DAA regimen is required. Treating patients at a younger age would also reduce the risk of DDI.

Keywords: Comorbidities, DDI, HCV, Japan

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Risk Assessment of Esophageal Variceal Bleeding in Patients with Liver Cirrhosis Using Acoustic Radiation Force Impulse Elastography-based Prediction Model: A Multi-center Retrospective Cohort Study

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Background/Aims: Periodic endoscopic screening for esophageal varices (EVs) is recommended for patients with liver cirrhosis. Acoustic radiation force impulse(ARFI)elastography can predict the presence of EV and high risk EV (HEV). We investigated whether ARFI-based prediction model can assess the risk of future EV bleeding (EVB).

Methods: In a 5-year period (2008-2013), a total of 242 patients with liver cirrhosis due to varying etiologies who underwent ARFI elastography and endoscopic surveillance for EV were recruited for retrospective analysisin two tertiary medical centers (Severance hospital and Kyungpook National UniversityHospital). The major end-point was the first EVB event. ARFI-spleen diameter to platelet ratio score (ASPS)was calculated [ASPS=ARFI velocity (m/s)×spleen diameter (cm)/platelet count (109/L)].

Results: The median age of the study population (156 men and 86 women) was 56.5 years. Hepatitis B virus was the most common etiology (n=157, 64.9%). The median ARFI velocity, spleen diameter, platelet count, and ASPS were 1.86 m/s, 10.0 cm, 146 109/L, and 0.11, respectively. Among all study participants, the optimal cutoff value was 0.15, a point maximizing the sum of sensitivity (90.5%) and specificity (61.1%)from receiver-operating characteristic (ROC) curves (area under ROC curve=0.758), and 90.0% negative and 90.0% positive predictive value by ASPS<0.13/ ASPS≥0.90 were provided for predicting the presence of EV at enrollment. Among patients with EV (n=72), 21 experienced their first EVBs during follow-up period (median 37 months). To differentiate EVBriskamong patients with EV, we divided them into ASPSlowEV group (ASPS <0.42) and ASPShighEV group (ASPS ≥0.42) according to ASPS 0.42, a point maximizing the sum of sensitivity (33.3%) and specificity (95.6%) from time-dependent ROC curves (area under ROC curve=0.731). ASPShighEV groupshowed significantly higher cumulative incidence rates of EVB than ASPSlowEV group(p=0.021 by log-rank test). Multivariate analysis found that higher ASPS(>0.42)was the only predictor of EVBamong patients with EV (hazard ratio 3.420, 95% confidence interval 1.043-9.983, p=0.042).

Conclusions: ASPS is a reliable predictor for the presence of EV and the future EVB risk. According to risk stratification, prophylactic treatments should be considered in patients with ASPS ≥0.42.

Keywords: Acoustic radiation force impulse, Esophageal variceal bleeding

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Validation of a Diagnostic Strategy of Combining Liver Stifness Value by Transient Elastography and Enhanced Liver Fibrosis to Assess Fibrotic Burden in Patients with Chronic Hepatitis B

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Background/Aims: Both liver stiffness (LS) values measured by transient elastography and enhanced liver fibrosis(ELF) test can assess fibrotic burden accurately. Recently, a sequential combination of LS value and ELF test has been proposed to ensurea higher chance to avoid liver biopsy (LB). In this study, we assessed the diagnostic performance of LS and ELF, validated LS-ELF diagnosticalgorithm,and investigated whether sequential combinationof LS and ELF performs better than their concomitant combinationin treatment-naïve patients with chronic hepatitis B (CHB).

Methods: In a 4-year period (2009-2013), a total of 290 patients with CHB who underwent LB, along with LS measurment and ELF test, were recruited for retrospective analysis. External cutoff value from Hong Kong study to predict both F3-4 and F4 were 6.0 and 7.5 for LS and 8.4 and 8.8 for ELF, respectively.

Results: The median age of the study population (men 144 and women 78) was 48 years. The median alanine aminotransferase level, HBV DNA level, LS value, and ELF test were 42 IU/L, 616,000 IU/L, 10.2 kPa, and 9.7, respectively. Advanced liver fibrosis (F3-4) and cirrhosis (F4) were identified in 23 (10.4%) and 118 (53.2%), respectively. Areas under the receiver operating characteristiccurve of LS value to predict F3-4 (0.887 vs. 0.703) and F4 (0.853 vs. 0.706) were significantly higher than those of ELF test (all p<0.001). The internal cutoff values to predict F3-4 and F4 were 9.0 kPa and 11.0 kPa for LS and 8.4 and 8.8 for ELF, respectively. Based on LS-ELF diagnostic algorithm, 60.4% (n=49) and 55.7% of patients (n=58) could avoid LB to exclude F3-4 and F4 using external cutoffs, respectively, whereas 71.6% (n=58) and 66.3% (n=69) of patients could avoid LB to exclude F3-4 and F4 using internal cutoffs, respectively. In addition, 78.7% (n=111) and 63.5% of patients (n=75) could avoid LB to confirm F3-4 and F4 using external cutoffs, respectively, whereas 68.0% (n=96) and 66.1% (n=78) of patients could avoid LB to confirm F3-4 and F4 using internal cutoffs, respectively. When LS-ELF diagnostic algorithm including confirmation and exclusion strategy was applied, 67.1-67.6% patients and 61.3-66.2% patients could avoid LB to diagnose F3-4 and F4, respectively, according to internal and external cutoff values, respectively. When the proportion of patients with correctly avoided LB in predicting F3-4 according to sequential LS-ELF diagnostic algorithm (69.4% by internal cutoffs and 72.5% by external cutoffs) was significantly higher than the proportionaccording tothe strategy of concomitant first-line use of LS and ELF which was proposed by Castera, et al (42.3% by internal cutoffs and 59.0% by external cutoffs) and Boursier et al (57.7%) (all p<0.05). Similar phenomenon was observed in predicting F4 (all p<0.05).

Conclusion: The performance of LS value by TE to predict F3-4 and F4 was significantly higher than those of ELF test. The diagnostic performance of LS-ELF algorithm was validated in our study and the sequential LS-ELF diagnostic algorithm performed significantly better than their concomitantfirst-line use in terms of higher chance to avoid LB in patients with CHB.

Keywords: Enhanced liver fibrosis, Liver stiffness

PE - 170

Body Mass Index as a Predictor of Severity of Fibrosis from a Tertiary Liver Center in the Philippines

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Aims: A variety of clinical and biochemical factors have been proposed to predict liver fibrosis. Some of these entail high cost and are impractical in the 3rd world setting. Thus, the aim of this study is to determine of body mass index (BMI) predectis the severity of liver fibrosis as assessed by Transient Elastography (TE, Fibroscan®), seen in a local liver clinic.

Methods: From 3207 patients seen at the Makati Medical Center Liver Clinic from Jan 2010 to Feb 2016 with various liver diseases, a total of 388 were enrolled into the study. Initial BMI and liver stiffness measurements (LSM) were obtained and subsequently followed up after patient education about lifestyle modification.

Results: Out of the 388 patients studied, the ratio of males to females was 1:1. The mean age was 53.27±12.3 years. The most common indication for TE was a diagnosis of non-alcoholic fatty liver disease (NAFLD) at 56.7%; followed by mixed liver disease, 39.5%; Hepatitis B, 3%; and Hepatitis C, 0.7%. Subsequent follow up showed no change in patients' BMI (26.7±3.68 vs 26.5±3.52, P>0.05). Likewise there was a positive correlation between the BMI and the LSM (P<0.05).

Conclusions: Our results showed that BMI may be a useful predictor of severity of fibrosis in patients with liver disease in the 3rd world setting where cost of fibrosis testing maybe prohibitive. This study likewise shows that patient education is a key factor in the reversal of fibrosis and that efforts to emphasize this are lacking.

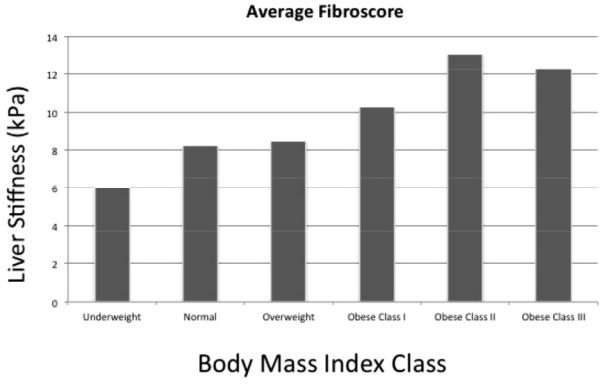

Table 1. Baseline characteristics of patients analyzed

Characteristics	No. (%) of patients
Sex	
Male	192 (49)
Female	196 (51)
Age (yr, mean±SD, range)	53.27±12.3 (19-84)
Diagnoses	
NAFLD	220 (56.7)
Mixed	154 (39.5)
Hepatitis B	12 (3)
Hepatitis C	3 (0.7)
BMI Class	
Underweight	3 (0.7)
Normal	123 (31.6)
Overweight	182 (46.7)
Obese Class I	58 (15)
Obese Class II	3(0.7)
Obese Class III	19 (4.8)

Keywords: Liver stiffness, Body mass index, Elasticity imaging techniques, Liver fibrosis

PE - 171

Recurrence Patterns of Curative Resected Ampulla of Vater Cancer: Significance of Lymph Node Dissection around Superior Mesentery Artery

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Purpose: Ampulla of Vater (AoV) cancer have better prognosis than other peri-ampullary cancers. However, prognosis of AoV cancer is different according to the stage, so it is necessary to establish treatment guideline according to the stage. Optimal treatment strategy must be based on tumor biology and recurrence pattern. The aim of this study was to figure out recurrence patterns of AoV ca. according to the stage and to suggest optimal treatment on AoV cancer.

Methods: From January 2000 to June 2012, 259 patients who underwent pancreaticoduodenectomy (PD) with R0 resection due to AoV cancer in Seoul National University Hospital were analyzed. Pylorus preserving PD (PPPD) was preferred, and lymph node (LN) dissection was performed around right side of superior mesenteric artery (SMA) and celiac axis. Survival and recurrence pattern was analyzed and its risk factors were explored.

Results: The mean age of total patients was 61.7 years and male to female ratio was 53:47. The median follow up duration was 40.7 month (range: 6-171) and 5 years disease free survival rate of total patients was 62.1%. Recurrence was occurred in 89 cases (34.4%) with 15.3 month median recurrence time. In 89 recurrence patients, total 149 recurrence sites were identified. The most common recurrence site was liver (n=52) in systemic recurrence and SMA LN in local recurrence (n=21). The risk factors of recurrence were poorly differentiated pathology (p=0.002), advanced T stage (0.032) and LN metastasis (p=0.010). Local recurrence was developed in 19 patients (21.3%), distant and both recurrence were 14 (15.7%) and 56 (62.9%) cases, respectively. Early T stage had a tendency of local recurrence especially around SMA, on the other hands, systemic recurrence was developed in advanced T stage (p=0.003). In above T2 stage, chemo therapy (CTx.) reduced recurrence, statistical insignificantly (5 year recurrence free survival rate in CTx (+) group: 62.2%, CTx. (-) group: 45.4%, p=0.072). In LN metastasis group, radio therapy (RTx.) reduced recurrence significantly (p=0.028), especially local recurrence (5 year local recurrence free survival rate in RTx. (+) group: 91.2%, RTx. (-) group: 57.9%, p=0.005)

Conclusion: Recurrence of AoV cancer after curative PPPD was 34.4%. Pattern of recurrence was different according to the T stage. Recurrence of T1 stage of AoV cancer was local recurrence especially SMA area LN. It need to be considered to dissect LN around SMA area. In above T2 stage recurrence was developed systemic pattern, therefore, adjuvant therapy need to be considered.

DAY 1: Thursday, June 16, 2016 (08:30-10:10) EAST TOWER Room AB

Basic Science Workshop 1

Intra and Extracellular Vesicle: Cell to Cell Cross Talk in the Liver

Chairs : Dae-Ghon Kim (Chonbuk National Univ.)
Kyun-Hwan Kim (Konkuk Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Exosome

Yong Song Gho

Department of Life Sciences, POSTECH, Korea

Communication between cells and environment is an essential process in living organisms. The secretion of extracellular vesicles, also known as exosomes and microvesicles is a universal cellular process occurring from simple organisms to complex multicellular organisms, including humans. Throughout evolution, both prokaryotic and eukaryotic cells have adapted to manipulate extracellular vesicles for intercellular communication via outer membrane vesicles in the case of Gram-negative bacteria and ectosomes (also known as microvesicles) or exosomes in eukaryotic cells. Recent progress in this area has revealed that extracellular vesicles play multiple roles in intercellular and interspecies communication, suggesting that extracellular vesicles are NanoCosmos, i.e., extracellular organelles that play diverse roles in intercellular communication (http://evpedia.info). This presentation focuses on the comprehensive aspects of mammalian and bacterial extracellular vesicles including components, biogenesis, and diverse functions that should facilitate further applications, especially to develop diagnostic tools, liver regeneration, and therapeutics including our recent progress in novel exosome-mimetic technology for targeted delivery of chemotherapeutics and siRNA as well as for adjuvant-free, non-toxic vaccine delivery system against bacterial infection.

Exosome and Liver Disease

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Exosomes are small membranous vesicles that originate from internal multivesicular bodies released by various types of cells. Exosomes have been found in body fluids such as plasma, urine, saliva, breast milk, and synovial fluid.[1] Exosomes contain cell-specific protein, mRNA, and microRNA.[2] Recent studies showed that exosomal microRNA is stable in blood because exosomes have a protective function against degradation from enzymes, such as RNAse.[3] Exosomal proteins and microRNAs can be functional and regulate cell signaling resulting in pathophysiology in target cells. It has been understood increasingly important that exosome can mediate cell to cell communication by transferring cargos to regulate cell activities such as protein expression, cell proliferation or differentiation, and antiviral responses in the recipient cells. Additionally, exosomal microRNA has a potential role as a diagnostic biomarker in patients with cancer.[4,5] This lecture summarizes recent exosome research in liver diseases mainly focusing on biomarkers of liver diseases including liver cancer.

We investigated the feasibility of using serum exosomal microRNAs as novel serologic biomarkers for hepatocellular Carcinoma (HCC).[6] We measured the expression levels of serum exosomal microRNAs in patients with hepatitis B virus (HBV)-related chronic hepatitis, liver cirrhosis (LC), and HCC. Serum exosomal microRNA was extracted from 500 μl of serum using an Exosome RNA Isolation kit. The expression levels of microRNAs were quantified by real-time PCR. The expression levels of selected microRNAs were normalized to *Caenorhabditis elegans* microRNA (*Cel-miR-39*). The expression of serum exosomal microRNAs in HCC patients were compared with those of patients with chronic hepatitis B (CHB) or LC. The serum levels of exosomal miR-18a, miR-221, miR-222 and miR-224 were significantly higher in patients with HCC than those with CHB or liver cirrhosis ($p < 0.05$). Further, the serum levels of exosomal miR-101, miR-106b, miR-122, and miR-195 were lower in patients with HCC than in patients with CHB ($p = 0.014$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Additionally, the serum levels of circulating microRNAs showed a smaller difference between HCC and either CHB or LC. Wang et al, reported that the expression level of serum exosomal miR-21 was significantly higher in patients with HCC than those with CHB or healthy volunteers.[7] Sugimachi et al. rencently reported that expression of miR-718 is significantly decreased in the serum exosome of patients with HCC recurrence after LT. They identified *HOXB8* as a potential target gene of miR-718, and its upregulation was associated with poor prognosis.[8] Collectively, these data suggest that serum exosomal microRNAs may have a potential for novel serologic biomarkers for HCC.

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Role of Autophagy in Liver Injury

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Autophagy is a genetically programmed, evolutionarily conserved intracellular degradation pathway involved in the trafficking of long-lived proteins and cellular organelles to the lysosome for degradation to maintain cellular homeostasis. It has been generally thought that autophagy serves as a cell survival pathway by removing damaged proteins and organelles such as mitochondrial and lipid droplets. We found that mice exposed to either acute alcohol or acetaminophen (APAP) induced autophagy process in the liver in both models. Autophagy serves as an adaptive mechanism to selectively remove alcohol-induced damaged mitochondria and excess lipid droplets. Pharmacological activation of autophagy protects against alcohol-induced steatosis and APAP-induced liver injury. The role of Parkin-mediated selective mitophagy and the role of p62 in selective autophagy for APAP-adducts will be discussed during the presentation.

DAY 1: Thursday, June 16, 2016 (10:30-12:10) EAST TOWER Room AB

Basic Science Workshop 2

Intra and Extracellular Vesicle: Cell to Cell Cross Talk in the Liver

Chairs : Kwan Sik Lee (Yonsei Univ.)
Jin-Wook Kim (Seoul National Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Autophagy in Chronic Viral Hepatitis

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The most common cause of hepatitis is by the infection of hepatotropic viruses. In particular, hepatitis B and C viruses (HBV and HCV) are well known to cause chronic liver disease. Persistent infection and pathogenesis of HBV and HCV depend on the ability of HBV and HCV to usurp various intracellular mechanisms of host cells against viral infection. Autophagy is a lysosome-associated catabolic process that is important for the removal of cytosolic components and impaired organelles to sustain cell homeostasis. Emerging evidences indicate that autophagy plays an important role in promoting the HBV and HCV life cycle in host cells. This process is also associated with innate immunity to remove intracellular pathogens. Here we review the relationship between autophagy and hepatitis viruses (HBV and HCV) and also discuss how autophagic process affects HBV or HCV pathogenesis. In particular, we focus on the role of mitochondrial dynamics involving mitophagic process (mitochondrial autophagy, mitophagy) during HBV and HCV infections.

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Regulation of Inflammasome Signaling and Its Potential Link to Metabolic Disorders

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Inflammasome is a cytosolic multiprotein complex to activate caspase-1 leading to the subsequent processing of inactive pro-interleukin-1-beta (Pro-IL-1) or pro-interleukin-18 (Pro-IL-18) into their active matured form. Inflammasome complex is assembled and activated only upon sensing of pathogen-associated molecular pattern (PAMP) derived from microbial infections or danger-associated molecular pattern (DAMP) derived from tissue injury. Once assembled, inflammasome complex plays a key role in innate immune defense against invading pathogens, but accumulating evidences also suggest that deregulation of inflammasome signaling contributes to the pathogenesis of many metabolic or neurodegerative disorders including type 2 diabetes, obesity, atherosclerosis and Alzheimer's disease. In this regard, the regulation of inflammasome signaling is of particular interest. Nod-like receptor family, pyrin domain containing 3 (NLRP3) is the best-studied inflammasome component, but it is still poorly understood how NLRP3 inflammasome is assembled and activated in response to a wide range of stimulations. Recently, the role of mitochondria has been increasingly suggested to modulate the activation of NLRP3 inflammasome. Here, we briefly summarize how the NLRP3 inflammasome contributes to the pathogenesis of metabolic or neurodegenerative disorders and how the mitochondria and its related intracellular organelles modulate the activation of NLRP3 inflammmasome.

Inflammasome in Liver Disease

Jong Eun Yeon

Korea University, Korea

Inflammasome (염증복합체)은 세포 내 존재하는 단백 복합체로, pathogen-associated molecular patterns (PAMPs) 혹은 damage-associated molecular patterns (DAMPs)에 의해 유발된 caspase를 통해 IL-1 β와 IL-18를 활성화된 형태로 전환시킨다. 관련된 질환으로는 NLRP3 변이와 관련된 CAPS (cryopyrin associated periodic syndrome), 통풍, 동맥경화, 비만 및 대사질환 등을 들 수 있다. 최근에는 간질환에서의 inflammasome의 역할에 대한 연구가 증가하고 있으며, 알코올성 간질환, 비알코올성 지방간 질환, 간섬유화 등이 그 예이다. 현재까지 임상적으로 승인된 치료제는 없으나 IL-1ß receptor antagonist (anakinra), glyburide, 25-hydroxycholesterol, probenecid, resveratrol, P2X7 antagonist 등이 inflammasome 활성화를 감소시킬 수 있다는 실험적 보고들이 있다.

색인단어: 지방간, 알코올성 간질환, 염증복합체, IL-1ß

1. Introduction

Inflammasome is a large, intracellular multi-protein complex that is a sensor of the endogenous or exogenous pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) that govern the cleavage of pro-inflammatory cytokines such as pro-interleukin (IL)-1β and pro-IL-18[1,2]. DAMPS including ATP, cytochrome C, fatty acid, hyaluronic acid, mitochondrial DNA, S100, HMBG1, particulate and crystals such as uric acid and cholesterol crystals may involve in the inflammasome activation cascade.[3] Examples of human disease associated with inflammasome pathways are NLRP3 mutation associated CAPS (Cryopyrin-associated periodic syndrome) characterized by recurrent fever and inflammation, gout and type II diabetes. In liver disease, alcoholic hepatitis, chronic HCV infection, ischemia-reperfusion injury, paracetamol-induced liver injury and nonalcoholic fatty liver disease were known to be involved in inflammasome activation.

2. Inflammsome related liver disease

1) Inflammsome activation in alcoholic fatty liver disease (ALD)

In patients with severe alcoholic hepatitis, serum levels of TNF, IL-8 and IL-1ß and PMN cells were substantially increased. As a consequence, activation of innate immune response and inflammation are major contributors to disease progression. Petrasek et al[4] reported that chronic ethanol administration to wild type mice induced steatosis, liver injury and increased hepatic expression of IL-1ß, pro-Casp-1, Asc and NLRP3. Using an IL1r-knock out mice and mice deficient in Casp-1 or Asc, they demonstrated that ethanol induced inflammasome and IL1-1ß activation were attenuated. Daily injection of an IL1r antagonist (IL1ra, anakinra) ameliorated liver inflammation. In ALD, gut-derived lipopolysaccharide, which signals through TLR4, is likely to be the first signal that induce IL-1 ß expression.[1]

2) Inflammsome activation in Nonalcoholic fatty liver disease (NAFLD)

Inflammasome activation was thought to link with obesity, metabolic syndrome, type II diabetes mellitus and NAFLD.[5,6] Csak et a[7] reported upregulation of inflammasome including NLRP3, ASC, pannexin-1 and procaspase-1 mRNA using MCD (methionine-choline defient) diet model and have shown increased caspase -1 activity and IL-1ß protein expression in steatohepatitis compared with control livers. According to their study, saturated fatty acid palmitic acid (PA) activates the inflammasome and induces sensitization to LPS-induced IL-1ß releases in hepatocyte. PA triggered danger signals from hepatocyte, in turn, activates and releases inflammasome, IL-1ß and TNF-α in liver mononuclear cell.

Hernao-Mejia et al[8] reported that inflammasome mediated dysbiosis regulates progression of NAFLD and obesity. In their study, NLRP6 and NLRP3 deficiency changes in the configuration of the gut microbiota, and leads to exacerbated hepatic steatosis and inflammation through influx of TLR4 and TLR9 agonists into the portal circulation, leading to enhanced hepatic TNF-α expression and drives NASH progression. Interestingly, co-housing of inflammasome deficient mice with wild-type mice results in exacerbation of hepatic steatosis and obesity. In our study[9] using HFD (high fat diet) induced NAFLD animal model, HFD caused glucose intolerance and hepatic steatosis. In mice fed an HFD with LPS, caspase-1 and interleukin (IL)-1β in the liver were significantly increased. Treatment with PPAR-δ agonist ameliorated the steatosis and inhibited overexpression of pro-inflammatory cytokines. In HepG2 cells, PA and LPS treatment markedly increased mRNA of several NOD-like receptor family members (NLRP3, NLRP6, and NLRP10[10]), caspase-1 and IL-1β. PA and LPS also exaggerated reactive oxygen species production. All of the above effects of PA and LPS were attenuated by PPAR-δ agonist.

3) Inflammsome activation in chronic HCV infection

HCV was sensed by multiple intracellular PAMPS such as RIG-I or TLR2, 3, 4, 7/8 and 9 and typically induced production of IFNs. Also, NLRP3, ASC and CASP-1 mediated IL-1ß activation was reported. In patients infected with HCV, monocyte inflammasome activation results in IL-18 production that in turn activate natural killer T cells.[11]

4) Liver fibrosis

Liver fibrosis related inflammasome activation can regulated directly by hepatic stellate cell (HSC) [12] or indirectly by kupffer cell.[13] Uric acid crystal can activates mouse HSC and results in induction of TGF-ß expression and collagen deposition. Gut derived PAMPs or hepatocyte derived DAMPs can activate inflammasome in Kupffer cell and Kupffer cell derived IL-1ß contributes to the activation of HSC. In alcoholic liver disease animal model, liver fibrosis was substantially reduced in Casp 1-knock out mice.[4] In NASH, steatosis and fibrosis were substantially reduced in IL-1r-defieinct mice fed with CDAA or high fat diet. In mice fed with MCD or CDAA diets, Casp-1 or Nlrp3 knock out improves liver fibrosis[13].

3. Therapeutic strategies in inflammasome related liver disease

Examples of signal I inhibitors, which is delivered by a number of TLR ligand and results in transcriptional upregulation of pro-IL-1ß and pro-IL-18, were eritoran (TLR4 inhibition) in severe sepsis, glycyrrhizin (HMGB1 inhibition) in acetaminophen (AAP)-, ischemia reperfusion (IR)-liver injury and chronic HCV infection, ethyl pyruvate (TLR4 inhibition) in IR injury, melatonin (TLR4 inhibition) in LPS induced liver injury and NASH, curcumin (TLR4 inhibition) in CCL4 induced liver injury and coronary artery bypass graft, IRS 954 (TLR7 and 9 inhibition) in AAP induced injury.[3] [14]

Inhibition of signal II, provided by a diverse range of molecules and results in assembly of inflammasome machinery, were P2X7 inhibition using apyrase (ATP depletion), etheno-NAD (NAD inhibition) and A438079 (P2X7 small molecule

antagonist) in AAP liver injury, allopurinol (xanthine oxidase inhibition) in AAP induced liver injury, febuxostat (xanthine oxidase inhibition) in IR induced renal injury, IDN-6556 (pancaspase inhibitor) in cholestatic liver injury and chronic hepatitis C, YVAD-CMK (selective caspase-1 inhibitor) in LPS/galactosamine induced liver injury, GS-9450 (oral capase 1,8,9 inhibitor) in NASH. Recombinant IL-1r antagonist anakinra has protective effect in murine model of IR, AAP induced liver injury.[4]

4. Conclusion

Inflammasome is known to have an important role in various spectrum of chronic liver disease including alcoholic-, non-alcoholic fatty liver disease, IR injury, drug induced liver injury and liver fibrosis. Targeting sterile inflammation may have therapeutic implication in future.

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DAY 1: Thursday, June 16, 2016 (13:10-14:50) EAST TOWER Room AB

Clinical Science Methodology Workshop 1

Real World Experience from Expert

Chairs : W. Ray Kim (Stanford Univ.)
Jung-Hwan Yoon (Seoul National Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

MELD: From an Idea to a Practice

W. Ray Kim

Stanford University School of Medicine, USA

When the MELD score was initially developed in patients undergoing elective placement of transjugular intrahepatic portosystemic shunt, out of a host of variables considered, a number of variables were found to be significantly associated with mortality in the univariate stage. These included, in addition to the current components of MELD (namely, bilirubin, creatinine, and INR), the cause of cirrhosis, ascites, hepatic encephalopathy, and albumin, as well as the Child-Turcotte-Pugh score. Of these variables, only three variables were subsequently selected as the score to be implemented in organ allocation policy.

Since MELD was adopted by OPTN, questions have been raised whether the score needs to be updated for patients waiting for transplantation, as opposed to the original patient sample of TIPS patients. It turned out that for all three variables, the existing coefficients underestimated the rapidity with which mortality increased. In addition, using different lower and upper bounds of the variables could attain some optimization of the score.

Several investigators have observed that hyponatremia may reflect mortality risk not adequately captured by the MELD score. When analyzed in conjunction with other measures of renal function, hyponatremia carries prognostic information independent of serum creatinine. However, when directly measured renal function was also taken into account, serum sodium became redundant – suggesting that serum sodium may reflect renal physiology that is not captured by serum creatinine.

Based on these data, several models to incorporate serum sodium into the MELD score have been proposed. Some features of interest in those models are (1) there are lower and upper bounds to serum sodium, beyond which mortality is not impact appreciably and (2) the impact of serum sodium is dependent of MELD in that hyponatremia is most important in patients with a low MELD score.

The impact of hyponatremia in patients undergoing liver transplantation on their postoperative outcome has been debated. Earlier studies linked hyponatremia with poor outcome including shorter survival and higher incidence of complications. More recent data indicate that there is no difference in survival between patients with hyponatremia and those with normal sodium. In contrast, patients with hypernatremia had a significantly higher mortality and early post-transplant complications.

In light of these data, incorporating serum sodium into the organ allocation scheme has been proposed. The Liver Simulation Allocation Model (LSAM) software has been utilized to predict implementation of such a system. When a number of models with MELD and sodium were compared with MELD score alone, the former models resulted consistently in lower waitlist mortality and fewer deaths after withdrawal, at the expense of marginal increase in post-transplant mortality. Taking into account serum sodium would result in lower overall mortality, including pre- and post-transplant deaths. Based on these data, MELD-Na* has been adopted for liver allocation in January 2016.

MELD-Na = MELD + 1.32(137-Na) - [0.033*MELD*(137-Na)]

RCT: From an Idea into a Practice

Young-Suk Lim

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The goal of clinical research is to draw inferences from the findings in the study about the nature of the population. The degree to which the investigator draws the correct conclusions about what happened in the study is the 'internal validity', and the degree to which these conclusions can be appropriately applied to people outside the study is the 'external validity' or generalizability. When we plan a study, we should design and implement a study to maximize the degree of internal validity. The best a researcher can do about the external validity is to ensure internal validity.
The basic structure of any form of clinical research is composed of 4 essential components. Study population, intervention of interest, comparison or control, and outcome. To ensure the internal validity, all these 4 components should be clearly defined and designed.
In terms of internal validity, randomized controlled trials (RCTs) are the gold standard for assessing the relationship between an intervention and an outcome, providing the highest level of evidence. One of the most important features of this study design is randomization, which ensures that the groups formed are similar, except for chance difference, in all aspects. Randomization reduces biases by making treatment and control groups "equal with respect to all features," except the treatment assignment. When randomization is performed correctly, differences in efficacy found by statistical comparisons can be attributed to the difference between the treatment and control.
'Investigator' is an individual who conducts an investigation. 'Sponsor' is an individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation. The sponsor is not the "funding organization" by FDA definitions. In these regards, the correct name of 'investigator-initiated trial (IIT)' should be 'investigator-sponsored trial (IST)'. In IST, the investigator has both responsibilities of investigator and sponsor.

The responsibilities of investigator defined by US FDA are as follows:
· Conduct study in compliance with GCP, protocol, & applicable IND/IDE regulations
· Ensuring informed consent of each subject is obtained (and retained)
· Personally conducting or supervising the investigation
· Protecting the rights, safety, and welfare of participants
· Ensure adequate medical care for the study participants
· Obtain necessary approvals from IRB
· Maintain and retain drug/device disposition and patient case history records
· Provide written reports to the IRB, as required
· Ensure changes are not implemented without prospective IRB/FDA approval
· Promptly report serious adverse events to the sponsor, IRB, and FDA
· Furnish Progress reports and Safety reports
· Ensure all study team members are informed about their obligations noted above

In addition to the investigator responsibilities, sponsor-investigators are also required to:
· Select qualified investigators at other institutions for multi-site trials
· Provide information to other investigators and study staff to ensure that the study is performed properly
· Ensure proper monitoring of the study
· Ensure the study is performed in accordance with the general investigational plan and protocol
· Submit necessary amendments/supplements to FDA
· Ensure that FDA and all participating investigators are promptly informed of significant new adverse effects or risks
· Maintain adequate records
· Maintain proper control of the study drug/device

Cohort Study: From an Idea into a Practice

Jeong Won Jang

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

One purpose of clinical research is to improve the transfer of scientific works into our clinical practice. By advancing the knowledge and technology base of clinical practice, research offers physicians and surgeons the opportunity to transfer ideas into clinical solutions. Due to the aggressive nature of diseases in our specialty, we are often confronted with various questions regarding optimal practices. Well-designed clinical researches are an important way to address the key questions that we are facing in daily practice. Randomized controlled trials, which have held the prominent position in evidence-based medicine, are not always indicated or ethical to conduct. Instead, observational studies are considered to be the next best method to address such questions. Three types of observational studies include cohort studies, case-control studies, and cross-sectional studies. Unlike cross-sectional studies (also known as prevalence studies) that examine diseases and exposure at one particular time point, case-control and cohort studies can offer specific advantages by measuring disease occurrence and its association with an exposure, thereby aiding in evaluating the cause and effect relationship.

A cohort study is one in which a group of subjects is studied over time (prospectively or retrospectively). Well-designed cohort studies can provide powerful results. Such studies are particularly advantageous for examining rare exposures because subjects are selected by their exposure status. Additionally, multiple outcomes can be assessed simultaneously. Disadvantages include the need for a large sample size and the potentially long follow-up duration resulting in a costly endeavor. A critical characteristic of patient selection is to include both the exposed and unexposed groups by effective sampling from the same source population. It is important to minimize loss to follow-up, as prospective cohort studies may require long follow-up periods. If too many patients are lost to follow-up, the internal validity of the study is reduced. Therefore, it is essential to select subjects who are able to be followed for the entire duration of the study.

For liver specialists, achievements in therapeutics for HBV diseases and improved outcomes of end-stage liver diseases from liver transplantation are a few examples of how our practice has been transformed in the last decades. It is highly likely that in the coming years we will see newer and innovative advances, which include anti-HCV therapies, molecularly/immunologically targeting drugs, gene editing, and precision medicine, etc. To be successful in our practice of the near future, we need to recognize unmet medical needs early enough that we are able to translate the data from well-designed studies initiated by our ideas on the key questions into solving the clinical problems that we face in our practice.

DAY 1: Thursday, June 16, 2016 (15:10-16:50) EAST TOWER Room AB

Clinical Science Methodology Workshop 2

Real World Experience from Expert

Chairs : Kengo Yoshimitsu (Fukuoka Univ.)
Han Chu Lee (Univ. of Ulsan)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

From an Idea into a New Device: MR Elastography

Kengo Yoshimitsu

Dept. of Radiology, Faculty of Medicine, Fukuoka University, Japan

Mechanical property of the human tissue is altered in many disease processes, most typically, presented as a change in the stiffness. Palpation, or manipulation is the most primitive, but useful form of applying this principle to medical examination, however, its target organs are of course limited to those located close to the skin, which physicians can touch. Magnetic resonance elastography (MRE) is an emerging imaging technology, in which propagation of acoustic shear waves, even if deep in the body, can be visualized as phase-shifts of protons utilizing the modified phase-contrast MR imaging technique; the wave length would be short in soft tissues, whereas in hard tissues, it would be long. In MRE, inversion algorithm is applied to calculate the stiffness of each voxel, and thus stiffness map or elastogram is generated.

The first application of MRE is for the liver in the assessment of grades of fibrosis. There have been several publications so far regarding this issue and excellent performance of MRE has been reported using pathological results as reference standards. In this lecture, basic principle, and current status of MRE including clinical data would be presented, along with several points to be kept in mind in clinical practice, and future perspectives as well.

From an Idea into a New Drug: Oltipraz

Yoon Jun Kim

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

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research on microorganisms and animals, filing for regulatory status to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug.

Drug discovery is a risky, costly and time-consuming process depending on multidisciplinary methods to create safe and effective medicines. An important goal of biomedical research is to translate basic research findings into useful medical advances. In the field of hepatology this requires understanding disease mechanisms as well as the effects of drugs and other compounds on liver function. Our hope is that this information will result in new or improved treatment for liver disease. Due to great progress in our understanding of the structure and functions of the liver and hepatotrophic viruses, the discovery of new drugs and their clinical development for many liver disorders has been increasing. We will focus on metabolic liver diseases, which affect millions, and yet have witnessed the fewest successes.

How to Prove Cost-effectiveness in My Research

Jeonghoon Ahn

Department of Health Convergence, Ewha Womans University, Korea

Cost effectiveness analysis (CEA) is frequently used in health technology assessment (HTA) and reimbursement decisions in many countries. A CEA study is important to show economic efficiency of innovation in medicine and will be a key component to design a sustainable healthcare system.

CEA combines net cost of health technology and the clinical effectiveness to measure economic efficiency such as how much money is needed to avoid a cardiovascular event or to extend patient life one more year. To estimate clinical effectiveness, systematic literature review is frequently used but clinical outcomes research using secondary data such as claims data or registry data is also used. Estimation of net cost is more problematic since the source of cost data is usually the claims data which include a lot of noises such as strategic coding to get reimbursement or high variability by practice patterns. Cost savings are reflected in net cost or incremental cost compared to an alternative health technology.

Because of the noisy cost data and the difference between efficacy and effectiveness, CEA and other economic evaluation methodology inevitably include large uncertainty. Hence, uncertainty analysis is the most important step make the art of rather arbitrary CEA calculation as a part of science. Ideally, all the possible combinations of parameters are tried to estimate the CEA results and they are summarized for how likely the intervention health technology is more cost effective than the alternative health technology. Probabilistic sensitivity analysis with 100,000 simulations and the percentages of the intervention technology become more cost effective than the alternative are usually presented in a good CEA research.

A couple examples including sorafenib vs hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma will be presented to help the audience to understand CEA.

DAY 2: Friday, June 17, 2016 (08:30-09:50) WEST TOWER Room AB

Symposium 1

Hepatitis C Virus

Chairs : Mark Sulkowski (Johns Hopkins Univ.)
Young-Hwa Chung (Univ. of Ulsan)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Appropriate Application of Direct Acting Antivirals

Mark Sulkowski

Johns Hopkins University, USA

Introduction. Five years after the first generation of direct acting antiviral (DAA) regimens gained notoriety for their complexity and treatment-limiting toxicity, multiple oral DAA regimens have been approved by the FDA with the promise of simple, well-tolerated, highly effective therapy. Early observations from large, "real-world" cohorts of patients treated with such regimens indicate that high rates of HCV cure can be achieved in clinical practice. Many observers have concluded that HCV treatment in the modern era is simple and, for many individuals with hepatitis C, this statement is correct. However, there is considerable heterogeneity with respect to the available HCV DAA regimens (> 5 are approved), the virus characteristics (genotypes, subtypes and other polymorphisms conferring resistance to DAAs and patient characteristics (advanced renal and liver disease). In this context, HCV treatment guidelines developed jointly by the American Association for the Study of the Liver (AASLD) and the Infectious Disease Society of America (IDSA) have a crucial role in helping patient and clinician navigate the path toward HCV cure.

Selection of the HCV DAA regimen. At this time, HCV treatment requires careful characterization of the individual patient and the patient's HCV infection. Important virus factors to consider include the magnitude of hepatitis C viremia (viral load) and HCV genotype and, in the case of genotype 1, subtype. In addition, depending on the HCV DAA regimen, persons infected with HCV genotype 1a may also require testing for the presence of HCV polymorphism in the NS5A region which confer decreased susceptibility inhibitors of NS5A, known as resistance associated variants (RAVs).

Similarly, as William Osler famously highlighted more than a century ago, "the good physician treats the disease; the great physician treats the patient who has the disease." Of particular importance is the presence or absence of cirrhosis since persons with cirrhosis are less response to DAA therapy and may require additional considerations for treatment. Further, HCV protease inhibitors – grazoprevir and paritaprevir – are not recommended in persons with decompensated cirrhosis due increased risk of liver injury. Other comorbid medical conditions must also be considered namely chronic kidney disease and, if ribavirin is considered, anemia. In addition to disease characteristics, an assessment of the likelihood of adherence to the HCV treatment regimen and the probability of HCV reinfection following cure. Patient who are at risk of reinfection should be considered high priority of HCV treatment due to the potential benefit to the individual and to others by prevention of HCV transmission. As such, risk of reinfection must not be used to deny access to treatment but rather to identify persons who will benefit from engagement in reduction strategies along with HCV DAAs.

HCV genotype 1. Multiple regimens have been approved by the FDA that are highly effective for the treatment of HCV genotype 1, leading to HCV cure in more than 95% of treated patients. However, the genotype 1 subtype must also be considered. Nearly all persons with HCV genotype 1b infection can be treated with interferon-free, ribavirin-free oral regimens whereas, with some DAA regimens, those with HCV genotype 1a infection may benefit from the addition of ribavirin. For example, in patients with HCV genotype 1a, the paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD) regimen led to HCV cure in 97% of patients when ribavirin was used compared to 90% of patients treated with PrOD alone.

In this population, ribavirin served to dramatically decrease the incidence of HCV breakthrough and post-treatment relapse and negated the impact of pre-treatment RAVs. As such, current recommendations are that all patients with genotype 1a receive ribavirin with PrOD. More recently, Elbasvir/Grazoprevir (EBR/GZV) was approved by the FDA for the treatment of HCV genotype 1a with ribavirin for 16 weeks if specific RAVs were detected prior to treatment at NS5A positions 28, 30, 31, or 93 and without ribavirin for 12 weeks if these RAVs were not detected. In contrast, the combination of ledipasvir/sofosbuvir is only recommended with ribavirin in the context of prior treatment experience and cirrhosis which may reflect the impact of NS5A RAVs in this population but not others such as treatment naïve patients.

Genotype 2. Based on a randomized controlled trial demonstrating improved safety, tolerability and efficacy, the single table regimen of sofosbuvir/velpatasvir is expected to replace sofosbuvir plus ribavirin as the recommended treatment for patients with HCV genotype 2.

Genotype 3. Many of the DAAs approved in the first wave of regimens are not particularly active against HCV genotype 3 infection (e.g., simeprevir, ledipasvir) and this strain of HCV appears of have unique characteristic particularly in the setting of cirrhosis that result in lower HCV cure rates with standard approaches to treatment. In 2016, based on the results of the ASTRAL-3 study, the expectation is the sofosbuvir/velpatasvir will emerge as the standard treatment approach for persons with this genotype 3 infection. However, some question remain about the role of ribavirin in the setting of cirrhosis and the role of NS5A resistance testing to detect the presence of the Y93H RAV which may be linked to greater risk of treatment failure.

Summary. While HCV treatment options will expand and simplify in 2016, health care providers have a crucial role is assessing the HCV-infected person and their virus to determine the most effective approach to achieving HCV cure.

Reading list

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Dietz J, Susser S, Berkowski C, Perner D, Zeuzem S, Sarrazin C. Consideration of Viral Resistance for Optimization of Direct Antiviral Therapy of Hepatitis C Virus Genotype 1-Infected Patients. PLoS One. 2015 Aug 28;10(8):e0134395. doi: 10.1371/journal.pone.0134395. eCollection 2015.

Current Strategy for Chronic Hepatitis C Treatment in Korea

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현재 한국의 C형간염 치료전략

정숙향

분당서울대학교병원 내과

Treatment of hepatitis C virus (HCV) infection is now facing a breakthrough arising from successful development the direct acting antivirals (DAA). Pegylated interferon alpha and ribavirin combination therapy for 24-48 weeks was a longstanding standard therapy despite high rate of adverse events and relatively low efficacy, showing sustained virological response (SVR) rate of 60% in genotype 1 and of 80% in genotype 2 HCV infected patients in South Korea. The first approved DAA therapy in Korea was daclatasvir and asunaprevir combination therapy for 24 weeks in 2015 with expected SVR rate of 80-90%. It is reimbursed for HCV genotype 1b chronic hepatitis and compensated cirrhosis patients in whom resistance associated variation (RAV) was not detected in NS5A region of HCV genome (L31 or Y93 codon). The next approved DAA therapy is ledipasvir/sofosbuvir fixed dose combination in one tablet and only reimbursed for genotype non-1b patients with expected SVR rate of 90-99% using 12-24 week regimen with or without ribavirin since May 2016. For genotype 2 infection, sofosbuvir and ribavirin combination for 12 weeks is approved with expected SVR rate of 95%. Under the resource restraint, DAA therapy is strictly regulated by National Health Insurance (NHI). However, at least for genotype 1b patients with baseline NS5A RAV or with decompensated cirrhosis, ledipasvir/sofosbuvir or other new DAA therapy should be reimbursed by NHI. In addition to the high cost, drug-drug interactions, and development of resistance associated mutants in DAA therapy are problems to overcome.

Keywords: Hepatitis C virus, Daclatasvir, Asunaprevir, Sofosbuvir, Ledipasvir

색인단어: C형간염, 간경변증, 항바이러스치료, 내성관련변이

C형간염바이러스(hepatitis C virus, HCV) 는 만성간염, 간경변증 및 간세포암종의 주요 원인이다. HCV는 우리나라 간경변증 및 간암 환자의 약 10-15%의 원인을 차지한다.[1] 아직 우리나라 인구를 대표하는 HCV 유병률은 알려져 있지 않지만, 2009년 국내 29개 검진센터에서 20세 이상 성인검진자 291,314명을 대상으로 당시 인구를 보정한 HCV 항체 유병률은 0.78%로 우리나라 성인 HCV 감염자 수가 약 29만명으로 추산할 수 있다.[2]

최근 개발된 direct antiviral agent (DAA) 경구약제 병합요법은 거의 부작용 없이 12-24주 치료로 90%에 달하는 치료성공률(sustained virologic response, SVR)을 보인다. 우리나라에서도 2015년에 인터페론 없는 경구 DAA병합치료가 처음 승인되었고 대한간학회에서는 DAA치료를 근간으로 하는 새로운 진료가이드라인을 2015년에 발표하였다. 이 가이드라인에는 현재까지 승인되지 않았으나 이미 미국이나 유럽을 위시한 다른 지역에서는 승인되어 사용경험이 축적된 약제들을 포함하였고, 유전자형별로 초치료자와 치료경험자를 구분하여 치료방법을 기술하였다.[3]

HCV 유전자아형 1a형과 1a형은 과거 인터페론 치료 시에는 치료반응에 차이가 없었으나 현재 DAA치료 시에는 약제에 따라 반응에 차이가 난다. 따라서 만성 C형간염 환자를 치료하기 위해서는 혈중 HCV RNA

농도 측정과 HCV 유전자형 검사 및 유전자형 1형의 경우 유전자아형이 1a인지 1b인지를 확인하는 검사를 시행해야 한다. 우리나라 환자에서 흔한 HCV 유전자형은 1b형(53%)과 2형(45%)이며, 유전자형 1a형은 약 3%, 유전자형 3, 4 및 6형이 각각 0.8%, 0.2% 및 1%로 보고되었고, 아직 유전자형 5형은 보고가 없다.[3]

DAA치료가 고가의 약제비용으로 인해 국가보험기준은 매우 제한된 약제 급여를 고시하고 있다. 2016년 5월 현재 국내에서 승인되고 의료보험급여로 처방이 가능한 DAA는 NS3/4A 억제제 asunaprevir (100 mg 정 하루에 2회 경구투여)와 NS5A 억제제인 daclatasvir (60 mg 정, 하루 1회 경구투여)와 병합요법, sofosbuvir (400 mg 1정 하루 1회 투여) 및 ledipasvir/sofosbuvir 고정용량 복합체(ledipasvir 90 mg/sofosbuvir 400 mg 단일 정제로 하루 1회 투여)이다. HCV 유전자형 1b형 만성 간염 및 대상성 간경변증 환자에서는 daclatasvir + asunaprevir로 24주간 치료하되 치료 전에 NS5A 내성관련변이 검사를 하여 L31, Y93 변이가 없는 경우에 치료를 시작한다.[4] 이 약제는 간독성이 있을 수 있어 비대상성 간경변증 환자에서는 금기가 되며 내성관련변이가 치료 전에 존재하거나 HCV RNA농도가 높을 경우 치료반응이 감소함에 유의해야 한다. 그러나 최근 일본에서 보고된 연구결과에 따르면 신기능 장애나 투석 중에 있는 환자에서 안전하게 높은 치료성공률이 보고되고 있어 이들 환자에서 사용가능 할 것으로 생각된다. HCV 유전자형 non-1b형에서는 ledipasvir /sofosbuvir로 12-24주간 치료하고 만성간염, 대상성 및 비대상성 간경변증과 간이식 전후의 환자들이 적용대상이 된다. HCV 유전자형 2형에서는 sofosbuvir+ribavirin 12주간 치료만이 급여적용이 된다. sofosbuvir 는 주로 콩팥을 통해 배출되므로 사구체 여과율이 30 mL/min 미만이거나 투석을 필요로 하는 말기 콩팥병 환자에서는 금기이다. 또 amiodarone과 병용투여시 심각한 서맥이 발생할 수 있어 금기이다.[5]

DAA들은 각 약제의 대사경로에 따라 간기능 및 콩팥기능 장애가 있는 경우 약제 사용에 제한을 받을 수 있으므로 각 약제의 특성을 이해하고 처방해야 한다. 또, DAA는 함께 투약하는 여러 약제들과 약제간 상호작용을 유발할 수 있어 치료 전에 이미 다른 질병으로 사용하고 있는 모든 약제에 대해 약제간 상호작용 여부를 확인하여야 하며, 치료 도중에 새로운 약제를 추가할 경우에도 상호작용을 확인하여야 한다. 약제간 상호작용에 대한 정보는 주요 웹사이트(예: www.hep-druginteractions.org)에서 얻을 수 있다.[3]

현재 유전자형 1b형 환자로 NS5A 내성관련변이 검사가 양성으로 확인되거나 비대상성 간경변증 및 간이식 전후의 환자일 경우 ledipasvir.sofosbuvir가 현재 급여기준으로는 의료 보험 급여대상이 되지 않아 치료비의 부담이 큰 실정이다. 과거 인터페론 기반의 치료경험이 있는 유전자형 2형의 간경변증 환자에서는 sofosbuvir 치료기간을 24주로 연장하는 것이 추천된다. 이러한 제한점은 향후 합리적으로 개선되어야 하며 새로운 약제들이 향후 추가적으로 우리나라에서도 승인이 되면 좀더 치료의 선택이 넓어질 것으로 전망한다.

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Towards IFN-free Treatment: DCV+ASV for Genotype 1

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유전자 1형 C형간염 치료를 위한 다클린자-순베프라 병합요법

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Introduction

Hepatitis C virus (HCV) infection is a major health problem worldwide affecting 130-170 million people leading to significant morbidity, mortality, and financial burden on healthcare. Approximately 80% of acute infections with HCV fail to clear spontaneously and progress to a state of chronic infection with serious long-term sequelae. Within 20 years of infection it is estimated that 60-70% of people with untreated chronic HCV infection will develop hepatic steatosis or fibrosis, up to 20% will develop cirrhosis, and up to 5% will progress to hepatocellular carcinoma[1]. HCV has a long and relatively symptom-free incubation period prior to causing serious illness. Therefore, most patients are diagnosed during the health check-up.

Until 2011, the standard of care of peginterferon and ribavirin combination produced an sustained virologic response (SVR, i.e., cuer of disease) rate of approximately 40-60% for HCV genotype 1 patients (48 weeks of therapy) and higher rate up to 80% for HCV genotype 2 (24 weeks of therapy). The limitaions of this regimen are well recognized. A number of side effects with peginterferon or ribavirin make patients to stop the treatment and to have insufficient dose of drugs that result in treatment failure. Several medical conditions such as liver cirrhosis, combined other diseases (autoimmune diseases, uncontrolled depression/diabetes, mental illness, thyroid disease, cardiopulmonary diseases, pregnancy, renal disease, etc) are not eligible for combination of peginterferon and ribavirin combination. This led to aggressive research into additional treatment targets and ways to predict patient response to treatment.

In the past 10 years, advances in HCV cell culture have enabled an improved understanding of HCV virology which has led to development of many new direct-acting antiviral (DAA) drugs that target key components of virus replication.

New hepatitis C treatments known as DAA therapies (e.g., sofosbuvir, daclatasvir, asunaprevir, simeprevir, ABT combinations, etc) are likely to require only 12-24 weeks of treatment, have minimal side effects and cure rates of over 90%, including in people with advanced liver disease or who have previously failed therapy. The remaining obstracles include access to appropriate care and treatment with lower drug price, and development of a vaccine. This review examines antiviral efficacy and safety of combination of daclatasvir (DCV) and asunaprevir (ASV), which is the first interferon-free, all oral regimen for the treatment of HCV genotype GT-1 in Korea.

Daclatasvir (DCV) plus Asunaprevir (ASV) for chronic HCV genotype 1b infection

Treatment of HCV has evolved and improved remarkably in recent years. The ongoing introduction of all-oral combination regimens of direct-acting antiviral (DAA) agents has resulted in significantly shorter treatment durations, better tolerability and higher rates of post-treatment sustained virologic response (SVR), a surrogate of cure, than earlier treatments based on the use of parenteral interferons. One such all-oral regimen combines daclatasvir (DCV) with asunaprevir (ASV). Daclatasvir is a nonstructural protein 5A inhibitor of hepatitis C virus (HCV) replication (One 60 mg tablet is taken orally once daily with or without food. If a reduced dose is needed, one 30 mg tablet is taken once daily).[2] Asunaprevir is an NS3/4A complex inhibitor of HCV replication (One 100 mg capsule is taken orally twice daily with or without food).[3] In combination, treatment with these two agents has produced high rates of SVR among patients infected with the GT-1b subtype, including treatment-naïve patients, patients medically ineligible for - or intolerant of - peginterferon alfa and ribavirin (pegIFN/RBV), and patients who had previously not responded to or relapsed on pegIFN/RBV treatment.[4-8] The combination of DCV + ASV has been approved in Japan and Korea for the treatment of HCV genotype GT-1 and is currently under regulatory evaluation in other countries.

The HCV pandemic in Asia differs from that in the West in several ways that may impact response to DCV + ASV or other new combinations of DAAs. Across much of Asia, the GT-1b subtype of GT-1 is the predominant HCV strain, whereas in North America and Northern Europe GT-1a is by far the most common. The spread of HCV in Asia also predates that in the West, resulting in a significantly higher proportion of elderly patients in countries such as Japan and Taiwan than in most Western countries, and a correspondingly higher incidence of cirrhosis and hepatocellular carcinoma.[9] Both older age and cirrhosis are historically associated with a higher burden of adverse events and poorer responses to interferon-based therapy,[10, 11] and their influence on response to newer oral regimens remains an area of great interest and research.

Treatment-emergent NS5A variants associated with drug resistance and virologic failure have been described for DCV and other inhibitors of HCV NS5A and may exist pre-treatment as naturally occurring polymorphisms whose prevalence may vary by region and subtype. For HCV GT-1b, two such resistance-associated polymorphisms (RAPs) for DCV have been observed at NS5A amino acid positions 31 and 93. On-treatment changes at these positions have been observed in both GT-1a and GT-1b virologic failures receiving DCV-containing regimens,[12-15] and their presence as pre-therapy RAPs that affect SVR to DCV + ASV has previously been observed in Japanese patients.[15] Two further NS5A changes at amino acid positions 28 and 30 have also been observed in GT-1a virologic failures receiving DCV-containing regimens and may also be present at pre-therapy baseline.[12,13]

In treatment-naïve HCV genotype 1b patients treated with daclatasvir and asunaprevir for 24 weeks, the SVR rate was 90%.[16,17] In this phase 3, multicohort study (HALLMARK-DUAL) at 116 sites in 18 countries, patients were adults with chronic HCV genotype 1b infection who were treatment-naive; previous non-responders to peginterferon alfa plus ribavirin; or medically ineligible for, previously intolerant of, or ineligible for and intolerant of peginterferon alfa plus ribavirin. This study included 307 treatment-naive patients (205 received daclatasvir plus asunaprevir and 102 received placebo; all randomly assigned patients received the intended treatment), 205 non-responders, and 235 ineligible, intolerant, or ineligible and intolerant patients. Daclatasvir plus asunaprevir provided sustained virological response in 182 (90%, 95% CI 85-94) patients in the treatment-naive cohort, 168 (82%, 77-87) in the non-responder cohort, and 192 (82%, 77-87) in the ineligible, intolerant, or ineligible and intolerant cohort. Serious adverse events occurred in 12 (6%) patients in the treatment-naive group; 11 (5%) non-responders, and 16 (7%) ineligible, intolerant, or ineligible and intolerant patients; adverse events leading to discontinuation (most commonly reversible increases in alanine or aspartate aminotransferase) occurred in six (3%), two (1%), and two (1%) patients, respectively, with no deaths recorded. Grade 3 or 4 laboratory abnormalities were uncommon, with low incidences of aminotransferase increases during the first 12 weeks with daclatasvir plus asunaprevir and placebo in treatment-naive patients (≤ 2% each).

Among Korean patients, 95% (20/21) achieved a SVR.[16,18] There were no differences in SVR rates based on sex, age, race, IL28B genotype, or presence of cirrhosis. However, multivariate regression analysis of baseline factors identified the presence of NS5A RAPs L31F/I/M/V and/or Y93H as negative predictors of SVR. Also, pooled data from five clinical studies of DCV and ASV in HCV genotype 1b patients show that the presence of the NS5A RAPs L31F/I/M/V and/or Y93H at baseline was associated with a reduced SVR (range: 36.9-41.9%), while SVR rates in the absence of these RAVs were high (range: 88.0-93.9%).[13,19] Pretreatment NS5A RAPs L31F/I/M/V and/or Y93H were present in 12.6-14.4% of HCV genotype 1b patients. Therefore, this combination is not recommended in patients with detectable NS5A RAPs L31F/I/M/V and/or Y93H at baseline.

Addition of the non-nucleoside NS5B inhibitor beclabuvir to daclatasvir and asunaprevir was predicted to overcome NS5A resistance and shorten treatment duration. DCV-TRIO is a fixed-dose combination consisting of 30 mg daclatasvir, 200 mg asunaprevir, and 75 mg beclabuvir taken orally twice daily.[20,21] The recent multinational, phase 3 study evaluated the all-oral, ribavirin-free, fixed-dose DCV-TRIO in patients with chronic HCV genotype 1 infection, with or without compensated cirrhosis in South Korea, Taiwan and Russia. 138 treatment-naïve and 31 treatment-experienced patients received twice-daily DCV-TRIO, for 12 weeks with 24 weeks of post-treatment follow-up. Twelve weeks of DCV-TRIO was well tolerated and provided 100% SVR12 in treatment-naïve and -experienced patients with HCV genotype 1 infection, with or without cirrhosis, including those with baseline NS5A resistance-associated polymorphisms. Table 1 shows major DAAs according to manufacturers which are already on sale or near at hand.

Conclusion

Combination of daclatasvir (DCV) plus asunaprevir (ASV) for chronic HCV genotype 1b infection is effective and relatively safe without baseline RAPs. Effective use of DCV + ASV as a treatment option in Asia requires an understanding of how RAPs and other influences of importance to Asian populations, such as older age and cirrhosis, affect treatment outcomes. Addition of beclabuvir to this regimen would be a promising and is at the corner for the market.

Table 1. Major DAAs according to manufacturers which are already on sale or near at hand.

Manufacturer	Protease inhibitors	NS5A replication complex inhibitors	Nucleotide NS5B inhibitors	Non-nucleoside NS5B inhibitors
Gilead	GS-9857	Ledipasvir* Velpatasvir	Sofosbuvir*	GS-9669
Merck (MSD)	Boceprevir* Grazoprevir*	Elbasvir* MK-8408 Samatasvir	MK-3682	MK-8876
AbbVie	Paritaprevir* ABT-493	Ombitasvir* ABT-530	-	Dasabuvir*
BMS	Asunaprevir*	Daclatasvir*	-	Beclabuvir

*: currently on sale

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Management of Direct Antiviral Agent Failures

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Failure to the combination of multiples Direct Antiviral Agents is relatively uncommon in the registration studies, with rates between 1 to 7% depending on patients baseline characteristics. In the real life treatment failure will, be higher probably related to a lower compliance. Treatment failure are usually related to relapse and less often on treatment viral breakthrough. HCV drug resistant variants are detected in the majority of patients who do not achieve viral eradication. The risk of developing these variants depends on host and viral factors, drug properties, and treatment strategies. Patients who carry resistance-associated variants do not obtain treatment benefits and are at risk of disease progression and transmission of the variants. The persistence of HCV drug variants depends of the type of RAVS, NS3-4A RAVs tends to disappear after stopping therapy while NS5A variants tend to persist for more than 2 years.

The best way to prevent emergence of resistant variants is to achieve viral elimination in the initial treatment with direct-acting antiviral drugs having different mechanisms of action, high antiviral potency, and genetic barriers. Combination therapies with sofosbuvir and NS5 inhibitors have been highly effective in patients failing first-generation protease inhibitors. By including ribavirin in the rescue regimen of patients with resistant NS3-4A variants, therapy can be shortened to 12 weeks. Optimal therapy for patients who fail an NS5A inhibitor and those with multidrug-resistant strains remains to be defined. Some preliminarily data suggest that some patients who failed to an NS5 A inhibitor can be rescued with the combination of simeprevir and Sofosbuvir or with longer therapy with sofosbuvir and ledipasvir, or the combination of 3D regimen plus sofosbviri and ribavirin for 24 weeks. In the interim, prudence is the best advice for patients with mild disease, and patients should wait for the results of drugs with greater activity against NS5A resistance.

Figure legends

Figure 1. Authorized combinations against HCV genotype 1 infection.

Current options for treatment of genotype 1 HCV infection include Pegylated Interferon (P) plus Ribavirin (RBV) with a protease inhibitor as Telaprevir (TVR), Boceprevir (BOC) or Simeprevir, or with a nucleotide analogue like Sofosbuvir (SOF). Interferon free regimens include the following options: 1) SMV plus SOF with or without RBV; 2) SOF plus an NS5A inhibitor like daclatasvir (DCV) or ledipasvir (LDV) in a fixed-dose combination; 3) an NS3-4A inhibitor, paritaprevir, boosted with ritonavir (paritaprevir/r) plus an NS5 inhibitor, ombitasvir (OBV), in a fixed-dose combination with a non-nucleoside polymerase inhibitor, dasabuvir (DSV). * Only for patients with cirrhosis if treatment is shortening to 12 weeks.

Figure 2. Factors more frequent identificated in DAA-based treatment failure.

In the phase-3 pivotal studies the main factors associated with relapse were as follow: 1) Factors related to the host: presence of cirrhosis (GT1 treated with SOF plus SMV or SOF plus DCV and GT3 treated with SOF plus DCV), male gender (SOF plus SMV and SOF/LDV), prior null responder to P/RBV (SOF plus SMV and 3D), IL-28B nonCC (SOF plus SMV and SOF/LDV) and previous failure to multiple DAAs combination (SOF/LDV); 2) Factors related to the treatment regimen: shorten duration of therapy (SOF plus SMV, SOF plus DCV and SOF/LDV), non addition of RBV (SOF plus DCV, SOF/LDV and 3D) and poor adherence (SOF plus SMV, SOF/LDV and 3D); 3) Factors related to the HCV: infection by genotype 1a (SOF plus SMV, SOF/LDV and 3D combination) or genotype 3 (SOF pus RBV), *baseline NS5A RAVs (only for patients with cirrhosis), and **presence of Q80K polymorphism (only for GT1a patients treated with SMV-based therapies).

Figure 3. SVR12, relapse rate and emerging RAVs after DAA-based treatment for HCV genotype 3.

None patients who relapse after SOF plus RBV therapy presented emerging NS5A RAVs. However, all patients who relapsed after SOF plus DCV presented NS5A RAVs: 6 at baseline (6 Y93H) and 10 emergent after treatment (9 Y93H and 1 L31I). Emerging RAVs was defined as S282T for patients treated with SOF plus RBV and any NS5A RAVs for patients treated with SOF plus DCV.

Figure 4. Recommended current salvage options for genotype 1 and genotype 3 treatment-experienced patients.
* The combination of SOF plus SMV is not recommended for genotype 1a-infected patients with Q80K polymorphism.

Key point Boxes

Introduction

- 170 million people live with chronic hepatitis C virus infection.
- The majority of patients who fail to triple therapy with Telaprevir or Boceprevir carry drug resistant strains in the hepatitis C virus NS3-4A region.
- The combination of direct-acting antivirals is currently the standard of care in many countries with SVR rates above 90% in the pivotal studies and around 80-85% in real-world setting.
- Failure to DAAs is mainly due to relapse, being virologic breakthrough during treatment rare.

Treatment strategies for patients infected by genotype 1.

- Sustained virologic response was similar in naïve patients independently of the presence of NS3-4A resistant variants variants at baseline.
- The determination of Q80K polymorphism is recommended prior to Simeprevir-based therapy in Genotype 1 a patients.
- Failures to multiple direct acting-antiviral regimens occur more often in GT1a patients with cirrhosis, GT3 treatment-experienced patients with cirrhosis, and patients receiving shorter therapy duration (<12 weeks).
- The presence of pre-treatment NS3-4A, NS5A, and NS5B resistance-associated variants do not seem to impact on SVR rates in naïve patients.
- NS3-4A resistance-associated variants tend to disappear after treatment discontinuation while NS5A and NS5B persist.

Management of antiviral failures.

- Genotype 1 patients who failed to triple therapy with protease inhibitors can be retreated with the combination of Sofosbuvir plus an NS5A inhibitor (Daclatasvir or Ledipasvir) or Sofosbuvir plus Simeprevir. Duration of therapy can be 12 weeks if ribavirin is added; otherwise the recommendation is 24 weeks.
- Genotype 3 patients who failed to Sofosbuvir plus Ribavirin can be retreated with Sofosbuvir plus Daclatasvir and Ribavirin for 12-24 weeks or Sofosbuvir plus Pegylated Interferon and Ribavirin for 12 weeks.
- Genotype 1 patients who failed to Sofosbuvir plus an NS5A inhibitor may carry resistance-associated variants to NS5A, which lead to decrease response to salvage therapy. These patients should wait for better drugs or combinations with DAAs without cross resistance probably including ribavirin.

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DAY 2: Friday, June 17, 2016 (13:10-13:40) WEST TOWER Room AB

Special Lecture 1.

Chair : Yung Sang Lee (Univ. of Ulsan)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Acute Kidney Injury in Cirrhosis

Florence Wong

University of Toronto, Toronto, Canada

Renal dysfunction is estimated to occur in almost 20% of admitted decompensated cirrhotic patients with ascites. The majority of cases of renal dysfunction in cirrhosis are acute in onset, and functional in nature with minimal or no structural renal damage. The recent recognition that renal dysfunction of a lesser degree of severity, compared to the prototypical hepatorenal syndrome (HRS) can also be associated with a negative prognosis, has led to the refinement of the definition of acute renal dysfunction in cirrhosis. In line with the Nephrology community, the term acute kidney injury (AKI) was adapted to describe acute renal dysfunction. The new definition uses a change in renal function rather than a static measure of renal function at any one time. The baseline serum creatinine (SCr) used to calculate the change in SCr, as well as various stages of AKI severity were also defined (Fig. 1).

Although AKI in cirrhosis can occur spontaneously, but is more likely to be precipitated by an event that disturbs the systemic and splanchnic hemodynamics. The most common precipitating event is bacterial infection, although other events such as loss of circulatory volume, be it GI blood loss or over diuresis, can also precipitate an episode of AKI. It is estimated that in infected cirrhotic patients who develop AKI, there is 80% chance of 30-day mortality, especially if the AKI episode progresses. In patients who completely recover from their AKI episode, their 30-day mortality is still higher than patients who have never developed an episode of AKI.

Once AKI has occurred, it is imperative that the precipitating event is dealt with, and the circulatory volume is replenished, preferably with blood products or colloid solutions. In patients who have volume responsive episodes of AKI, the SCr should return to baseline levels. In patients who have at least stage 2 AKI, consideration should be given to start vasoconstrictor therapy (Fig. 2) together with albumin. Terlipressin has been the main stay of treatment for volume non-responsive episodes of AKI, especially in Europe and Australia. In countries where terlipressin is not available, norepinephrine has been proven to be equally efficacious as terlipress in reversing AKI, but the midodrine and octreotide combination has been shown to be inferior to terlipressin in reversing AKI. Type 1 hepatorenal syndrome as defined by the International Club 20 years ago, is a special form of AKI, and management should follow the same algorithm. Cirrhotic patients who develop AKI should be assessed for liver transplantation, especially if liver dysfunction is also present. Reversal of AKI pre-transplant will yield post-transplant survival similar to that of patients who receive a transplant without a history of AKI.

Given the fact that cirrhotic patients with decompensation are at risk for the development of AKI, efforts are now being made to find biomarkers that can identify patient susceptibility for AKI, detect early reduction in GFR, indicate mechanism of injury, and track progression of AKI. Until these biomarkers are available, every effort should be made to prevent the development of AKI in cirrhosis.

Parameter	Definition
Baseline SCr	Stable SCr ≤ 3 months If not available, a stable SCr closest to current one If no previous SCr at all, use admission SCr
Definition of AKI	↑SCr ≥ 26.4μmol/L (0.3mg/dL) in ≤48 hours, or ↑50% from baseline
Staging	Stage 1: ↑SCr ≥26.4μmol/L (0.3mg/dL) or ↑SCr ≥1.50-2.0 X from baseline Stage 2: ↑SCr >2.0-3.0 X from baseline Stage 3: ↑SCr >3.0 X from baseline or SCr ≥ 352μmol/L (4.0mg/dL) with an acute ↑≥26.4μmol/L (0.3mg/dL) or initiation of renal replacement therapy
Progression	Progression of AKI to a higher stage, or Need for renal replacement therapy
Regression	Regression of AKI to a lower stage
Response to treatment	None : No regression of AKI Partial: Regression of AKI stage with a ↓in SCr to a value ≥0.3mg/dL above baseline Complete: ↓SCr to <0.3mg/dL from baseline

Figure 1. Revised definition of AKI for cirrhosis

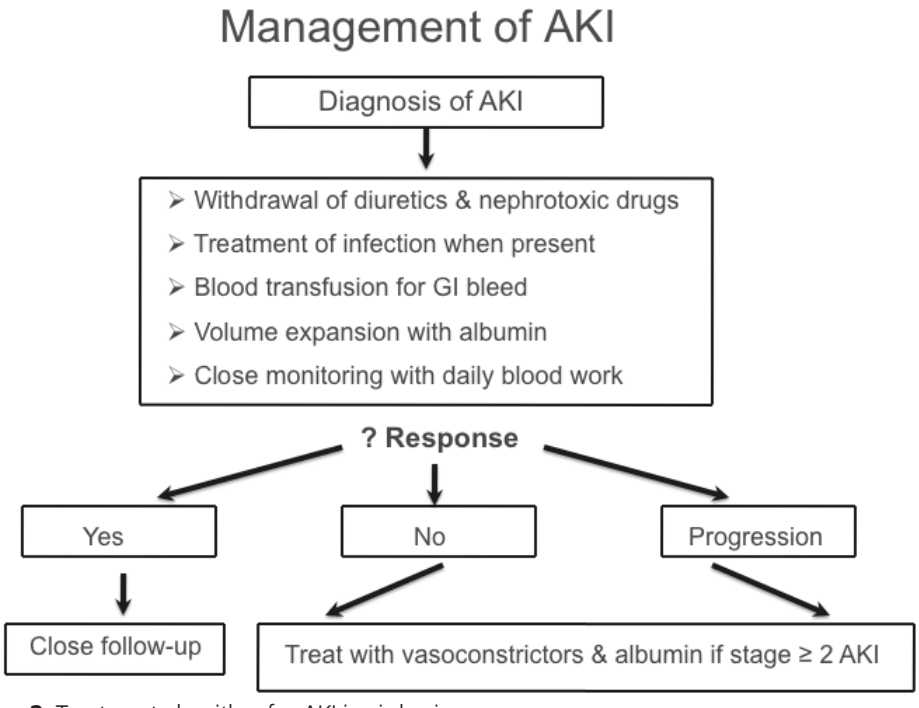

Figure 2. Treatment algorithm for AKI in cirrhosis

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DAY 2: Friday, June 17, 2016 (13:50-15:30) WEST TOWER Room AB

Clinical Hepatology Update

Chairs : Haak Cheoul Kim (Wonkwang Univ.)
Young Oh Kweon (Kyungpook National Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Clinical Hepatology Update: Changes of DDLT Waiting Priority in Korea

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뇌사자 간이식을 위한 간장 응급도 변경

김 명 수

연세대학교 의과대학 외과학교실

2012년 및 2014년 질병관리본부 정책연구용역사업의 결과로 국내에서 적용되는 뇌사자 간장 응급도 기준이 변경되어 2016년 6월(추정)부터 시행될 예정이다. 새로운 장기배분원칙은 MELD/PELD 점수를 기반으로 기존의 지역별, 혈액형별 우선순위를 조정하여, 간장 응급도가 높은 환자에게 간장이 배분되도록 개발되었다.

주요한 내용은 아래와 같다.

1. MELD/PELD 점수에 따라서 응급도 2(38-40), 응급도 3 (31-37), 응급도 4 (21-30), 응급도 5 (≤20)으로 나눈다.
2. MELD/PELD 점수는 UNOS 규정에 따른 점수계산에 의거한다.
3. 응급도 1 는 기존의 Status 1에 준하나, 응급도 1의 조건이 엄격해 짐. 14일간 등록이 가능하며, 14일 이후에는 MELD/PELD 점수에 따라서 응급도 2 이하로 배정된다.
4. 간세포암이 동반된 환자는 MELD점수에 따라서 4점(MELD 0-13점) 혹은 5점(MELD 14-20점)의 추가점수를 부여한다. MELD 점수가 20점 이상인 경우에는 추가점수는 없다.
5. 재등록이 필수사항입니다. 응급도 2-3 (7일), 응급도 4 (3개월), 응급도 5 (6개월)의 재등록이 필요하며, 재등록기간이 경과된 이후에는 MELD점수는 6점으로 간주한다.
6. 응급도 2 는 각 MELD 점수별로 동일혈액형을 우선 배정이며, 응급도 3 이하에서는 응급도내에서 동일혈액형을 우선 배정한다.
7. MELD 점수가 같은 경우에는 계산되는 대기시간은 현 멜드점수 등록시간에 따라서 장기별 점수가 부여된다.
8. 예외적인 MELD점수 부여와 특수한 경우의 등록여부는 간장분과위원에서 결정한다.

변경된 응급도 기준에 따른 뇌사자 간장배분의 형태가 어떻게 개선되는지에 대한 평가가 필요할 것으로 판단되어, 2016년 정책과제로 간장 응급도 기준의 변경 후 간장 배분 양상과 간이식 대기자의 대기시간의 변동사항을 비교함으로서 간장 응급도 기준변경의 효과를 검증하고자 한다.

Diagnosis of Sub-centimeter Sized Hepatocellular Carcinoma

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With active implementation of a surveillance program for high-risk HCC patients, small HCC with atypical vascular pattern (e.g. HCC with only arterial hyperenhancement) or early HCC with no arterial hyperenhancement is being detected with increasing frequency. However, based on HCC criteria proposed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD), a diagnosis of HCC is achieved only for nodules 1 cm or larger in diameter showing typical vascular pattern (i.e., intense arterial enhancement and then washout). As far as hepatocellular nodules showing an atypical vascular pattern or smaller than 1 cm are concerned, diagnoses still rely on a positive biopsy or are proposed for careful follow-up. Gadoxetic acid is widely employed liver MR contrast agent for HCC workup. The most strongpoint of this agent is to show HCC as being hypointensity on hepatobiliary phase. Therefore, arterial only enhancing small HCC without washout on conventional dynamic MRI or CT can easily be characterized by using hepatobiliary phase. In addition, hypovascular early HCC can be depicted only on hepatobiliary phase. Adding diffusion weighted imaging and T2-weighted imaging to gadoxetic acid-enhanced MRI is helpful to characterize small HCC (< 1cm) or early HCC by differentiating it from dysplastic nodule.

Keywords: Small hepatocellular carcinoma, Magnetic resonance imaging, Gadoxetic acid, Diffusion-weighted imaging, Diagnostic criteria

서론

최근 만성간질환 환자에서 발견되는 국소 간병변 진단을 위해 자기공명영상이 널리 이용됨에 따라 과거에 비해 크기가 작은 간 종양의 발견이 증가되었고 이로 인해 종양의 감별진단을 위한 영상검사의 중요성이 더 강조되고 있다. 간세포암진단을 위해 국내에서 널리 사용되고 있는 MRI 조영제인 Gadoxetic acid는 고식적인 세포외액조영제가 제공하는 혈류정보 외 에 간세포시기를 제공함으로써 1 cm 이하 소간세포암의 발견 및 진단을 용이하게 한다. 또한 최근 널리 이용되고 있는 확산강조영상을 gadoxetic acid 조영증강 MRI 와 함께 사용하면 소간세포암이나 조기 간세포암의 진단에 더 큰 도움을 받을 수 있다.

본론

간 컴퓨터 단층촬영(CT) 이나 자기공명영상(MRI)의 기술의 발전과 화질의 향상은 간세포암의 영상진단 정확도의 증가와 조기 검출의 향상을 가져왔으며 현재는 병리적 진단 없이 HCC를 진단할 수 있는 영상진단기준이 확립되어 널리 사용되고 있다. EASL (the European Association for the Study of the Liver)과 AASLD (the American Association for the Study of Liver Disease) 에서 제시하는 영상진단 기준은 CT나 MRI의 혈역동학적 정보 (동맥기 과혈관성과 문맥기나 지연기에서의 조영제의 씻김)에 의존하여 1 cm 크기 이상의 간세포암만 진단할 수 있다[1,2]. 바꾸어 말하면 1cm 미만의 간세포암은 CT나 고식적인 MRI 상 전형적인 혈역동학적 소견이 보이지 않을 가능성이 많으며 간세포암 이외의 이형성결절이나 간동정맥 단락(arterio-portal shunt) 등의 결절과 감별이 어려움을 의미한다. 또한 일부

전향적 연구[3]에 의하면 간경화환자 에서 발견된 1 cm 이하의 결절은 간세포암(14.6%)보다는 재생결절이나 이형성결절, 혈관종일 가능성이 더 높으니 추적 관찰이 권장된다 하였다. 2008년부터 국내에서 널리 사용되고 있는 간특이 MRI조영제인 gadoxetic acid (Gd-EOB-DTPA; Primovist, Bayer Healthcare, Berlin, Germany)는 한번의 조영제 주입으로 고식적인 가돌리늄 조영제를 사용했을 때와 유사한 초기 역동기영상을 제공하고 지연기 영상에서는 간세포특이 조영제의 특성을 보여주어 국소 간 병변의 검출 및 진단율의 향상을 가져 올 수 있는 장점이 있고[4] 많은 연구들은기존의 CT 나 고식적인 가돌리늄조영제를 사용한 MRI 보다 우수한 간세포암 검출율을 보여주었다[5-7]. 2014년에 개정된 대한간암연구학회의 진단 가이드라인에서는 gadoxetic acid 조영증강 MRI를 간세포암 진단기준에 도입하였으며 작은 국소간질환의 검출에 장점을 지닌 gadoxetic acid 조영증강 MRI 의 도입은 1 cm 이하의 간세포암의 진단을 가능하게 한다. 대한간암연구학회의 진단 가이드라인에 의하면 1cm 이하의 간세포암의 경우 두가지 이상 CT 와 MRI 검사에서 간세포암의 조영증강기준 (동맥기 과혈관성과 문맥기나 지연기에서의 조영제의 씻김)을 만족하고 간염이 잘 조절되고 있음에도 지속적인 AFP 상승이 있을 때 진단할 수 있다[8-9]. 마찬가지로 최근 JSH (the Japan Society of Hepatology)에서도 간세포시기를 간세포암 진단기준에 도입 하였으며 미국영상의학회의 간세포암 보고체계인 LI-RADS (Liver Imaging-Reporting and Data System) 2014년 개정판에서도 간세포시기를 간세포암의 보조 진단기준으로 도입하였다[10].

하지만 개정된 대한간암연구학회의 진단 가이드라인에서는 gadoxetic acid 의 20분 간세포시기는 언급이 없으며 고식적인 세포외액조영제와 마찬가지로 문맥기나 조영제 주입후 2분 - 3분의 지연기영상에서의 씻김현상을 진단기준으로 삼고 있으며 이는 대부분의 양,악성국소 간질환은 20분 간세포시기에서 저신호강도로 보임을 감안하여 위양성을 줄이기 위함이 목적이다. 하지만 gadoxetic acid 의 경우 조영제 주입후 1분 정도부터 간세포에 섭취되어 세포외액조영제의 역동기와는 약간 다른 조영증강 양상을 보이며 20분 지연기영상에서 저신호강도로 보이는 간세포암 대부분은 3분 지연기에서도 유사하게 보인다. 일부 연구[11]에서는 20분 간세포시기를 제외한 3분 영상까지만을 간세포암 진단기준으로 삼으면 20분 간세포시기를 포함할때 보다는 민감도는 낮지만 특이도가 상대적으로 높아져 높은 진단정확도를 유지할 수 있음을 보였 주었으나 최근 보고된 연구[12]에서는 2 cm 이하 크기의 만성간질환 환자에서 발견된 간결절을 대상으로 gadoxetic acid 조영증강 MRI 상 동맥기 고혈관성과 20분 간세포시기 저신호강도의 진단기준이 문맥기나 3분 지연기영상에서의 저신호강도를 사용한 EASL 진단기준 보다 높은 민감도를 보여준 반면 유사한 특이도를 보여주어 20분 간세포시기의 중요성이 점차 대두 되고 있다.

고식적인 세포외액조영제를 사용한 CT 나 MRI 검사에서 1cm 이하의 작은 간세포암은 동맥기에서는 조영증강을 보이나 문맥기나 지연기에서 씻김 현상을 동반하지 않는 경우가 많아 간경화에서 매우 흔하게 보이는 동정맥 단락 (arterio-portal shunt)과의 감별이 어렵다. Gadoxetic acid 의 간세포시기뿐 아니라 문맥기나 3분 지연기는 이러한 작은 HCC 를 저 신호강도로 보여 줌으로써 동정맥 단락과의 감별을 용이하게 해주어 1cm 미만의 HCC 진단을 가능하게 해준다[4].

Gadoxetic acid 의 간세포시기의 또 하나의 장점은 고식적인 CT 나 MRI 에서는 보이지 않는 동맥기 고혈관성을 가지지 않는 작은 결절을 간세포시기에서만 보여줄 수 있다는 점이다. 많은 연구를 통해 이들은 이형성결절(dysplatic nodule, DN)이나 조기간세포암임이 밝혀졌으며 이들을 추적관찰시 동맥기 고혈관성을 가지는 전형적인 간세포암 소견으로 변할 수 있음이 여러 연구들을 통해서 밝혀졌다 . 이런 결절의 크기는 0.4 - 4.0 cm으로 보고되었으며 이는 상당수의 1 cm 이하 크기의 저혈관성의 조기간세포암이 포함되어 있음을 의미한다. 이러한 결절은 크기가 10 - 15mm 이상일 때, 지방을 포함할 때, T1강조영상에서 고신호강도 일때, T2강조영상이나 확산강조영상에서 고신호강도를 보이거나 추적 관찰시 성장속도 빠를 때, 추후 고혈관성의 간세포암 소견으로 변할 가능가능 높은 것으로 보고 되었다. 이러한 저혈관성의 간세포시기 저신호강도 결절이 고혈관성 간세포암 소견으로 진행할 수 있는 1년 누적비율 (cumulative rate)은 3.2% - 30.4% 로 보고마다 다양하다[13,14]. 이런 현상은 다단계 분화설(multistep hepatocarcinogenesis)을 통한 간암발생으로 해석되며 간세포암 진단에 gadoxetic acid 의 도입은 진행성 간암의

전구단계의 조기인지를 가능하게 함을 의미한다. 최근 연구에 의하면 이러한 결절은 간절제술이나 고주파소작술후 다발성 재발암의 원인으로 증명되었다. 하지만 추적 관찰시 이러한 간세포시기 저신호결절에서만 전형적인 고혈관성 간세포암이 발생하는 것은 아니고 특이 소견이 없던 다른 간실질에도 고혈관성의 간세포암이 생길 수 있으며 간세포시기 저신호결절을 가진 간은 이런 결절이 없는 간에 비해 더 흔하게 간세포암 발생이 보고 되었다[15].

만성간질환환자에서 생긴 간세포결절이 T2강조영상과 확산강조영상에서 고신호강도를 보일때는 간세포암을 시사하는 소견이다. 일부 고등급이형성결절도 고신호강도를 보일수 있으며 병리진단상 조기간세포암과 고등급이형성결절과의 감별이 명확하지 않는 경우가 있음을 감안하면 영상만으로 간암발생의 중간단계의 결절의 명확한 감별은 현실적으로 불가능하다. 확산강조영상은 최근 간MRI 의 기본 검사로서 널리 사용되고 있으며 높은 간-종양 대조도를 보여주어 소간세포암의 검출에 큰 장점을 보여주고 있다[16]. 간세포암 진단시 gadoxetic acid 나 고식적인 가돌리늄조영제를 사용한 조영증강영상과 확산강조영상의 조합은 간세포암 진단, 특이 1 cm 이하의 간세포암 진단에 유용할수 있음이 보고되었으며 이는 확산강조영상은 1cm 미만의 매우 작은 간결절의 발견을 용이하게 하고 동맥기상 조영증강이 되지 않는 저혈관성 조기 간세포암이나 동맥기에서만 조영증강되는 작은 간세포암 진단에 도움을 줄 수 있음을 의미한다[16-18].

결론적으로 간 자기공명영상은 병변의 T1, T2강조 정보를 제공하고, 세포외액조영제외에 gadoxetic acid와 같은 간 특이조영제를 사용 할 수 있고 확산강조영상을 통해 작은 간종양 검출 및 진단을 가능하게 하며 다양한 정보를 동시에 제공하는, 다른 영상기법과는 차별화된 영상으로서 1 cm 미만 크기의 소간세포암이나 조기 간세포암 진단에 큰 장점과 잠재력을 가진 기법이라 할 수 있다. 하지만 1 cm 이하의 소간세포암의 조기치료가 전체생존율 (overall survival)을 향상 시킨다는 근거가 될만한 연구는 아직 없다. 저혈관성의 조기 간세포암의 치료는 진행성간암 치료군과 비교시 생존율을 크게 향상시키지 못한다는 연구[19]나 진행성간세포암과 조기간세포암의 동시치료는 무재발생존율 (recurrence free survival)은 증가시키나 전체생존율 은 증가시키지 못한다는 보고[20]는 소간세포암이나 조기 간세포암의 치료에 회의적인 시각을 제공할 수 있다. 또한 최근에 나온 일부 연구에서는 고주파치료가 간세포암의 악성도의 증가나 다발성 간세포암의 증가를 유발시킨다는 보고[21]도 있어 소간세포암의 적극적인 치료에 대해서는 향후 많은 연구가 필요하다[22].

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Nonalcoholic Steatohepatitis: Diagnosis and Treatment Update

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비알코올지방간(non-alcoholic fatty liver, NAFL)은 단순지방간(simple steatosis)과 간내 지방의 침착과 염증 및 간세포의 풍선화(ballooning)를 동반하는 지방간염(steatohepatitis, NASH), 및 비알코올지방간 연관 간경변증을 모두 포함하는 '질환군'을 명칭한다. 우리나라의 경우 지방간의 유병율은 25-30% 정도로 추정하고 있으며,[1] 이 중 10-15%는 염증을 동반한 지방간염으로 추정하고 있다. 임상에서 문제가 되는 것은 염증과 섬유화를 동반한 지방간염이며, 지방간염의 일부는 간경변증과 간암으로 진행된다고 알려져 있다.

최근 비알코올지방간 질환(non-alcoholic fatty liver disease, NAFLD)이 사회적으로 이슈가 되는 이유는 첫째, 비알코올지방간의 유병율이 급격하게 증가함에 따라 이와 연관된 사회적 비용(검사, 치료)이 급격하게 증하고 있다는 점이다. 최근 10년간 비알코올지방간 질환과 연관된 약물시장의 규모는 매년 15%씩 증가하고 있다. 둘째, 만성간질환에서 감염성 질환인 B형 및 C형 바이러스 간염에 대한 유병율 감소 및 치료 성적의 향상으로 만성 간질환에서 비알코올지방간 질환이 차지하는 비중이 커졌다. 마지막으로 비알코올지방간 질환은 간질환 뿐 아니라, 심혈관질환 및 당뇨병 발생을 의미 있게 증가시켜 사회적 부담으로 작용한다는 점이다.

비알코올지방간 질환에서 해결되지 않은 문제는 조직생검을 대체할 수 있는 효과적인 진단방법이 아직 확립되지 않았다는 점과 아직 만족할 만한 치료방법이 없다는 점이다. 본 연제에서는 비알코올지방간 질환에서 현재 제시되고 있는 진단방법과 치료방법에 대하여 기술하고자 한다.

1. 비알코올지방간 질환의 진단 (영상학적 방법)

1.1 복부 초음파

복부초음파는 임상에서 지방간을 진단하는데 가장 널리 사용되는 방법이다. 비교적 비용이 비싸지 않으며, 간내 지방이 33% 이상인 중등도의 지방간을 진단하는 민감도가 93%로 우수하다.[2] 그러나 특이도가 낮다는 단점이 있으며 간내 지방량이 30% 미만인 경우 민감도가 낮다는 단점이 있다. 또한 초음파를 시행하는 검사자에 따라 진단의 편차가 있다는 단점이 있다.[2]

1.2 복부전산화 촬영

조영 증강을 하지 않은 복부 전산화 촬영을 통하여 간내 지방량과 비장의 지방량을 이용하여 지방간의 유무를 예측할 수 있다. 복부전산화 촬영을 하게 되면 영상을 Hounsfield unit (HU)라는 단위를 이용하여 얻어진 이미지 영상을 표준화 하게 된다. 공기의 경우 -1000 HU, 물의 경우 0 HU, 뼈의 경우 1000 HU로 하여 각 조직의 영상의 감쇄 정도를 표준화 하게 된다. 일반적으로 간의 경우 비장이나 혈관 및 담도 보다 밝게 보이며 60±10 HU을 보이게

되며, 피하지방의 경우 -90 HU를 나타낸다. 간에 지방의 침착이 많아지게 되면 간의 HU가 비장의 HU 보다 낮아지는 현상이 발생된다. 일반적으로 간의 HU가 ≤ 40 HU 미만이거나 간과 비장의 HU의 차이(liver minus spleen density difference)가 -10 HU 보다 작은 경우 또는 간과 비장의 비율(liver/spleen ratio)이 ≤ 0.9 미만인 경우 지방간으로 진단한다.[3] 그러나 방사선의 피폭이 발생한다는 단점과 CT 기계 회사 및 설치 기관의 셋팅에 따라 측정값이 달라질 수 있다는 점, 부종 또는 구리 등의 침착에 의하여 영상학적 밀도의 감쇄량이 달라질 수 있으며, 초음파와 비교하여 민감도가 더 우수하지 않다는 문제점이 있다.

1.3 MRI를 기반으로 하는 검사 방법 (MRS, multi-parametric quantitative MRI)

지방에 있는 수소와 물에 존재하는 수소는 각각 서로 다른 특이한 공명을 가지고 있으며 이러한 원리를 이용하여 최근 간내 지방의 양을 측정하는 MRI를 기반으로 하는 다양한 방법이 소개되고 있다. MRS 및 six echo를 이용한 multi-parametric fat MRI의 진단의 민감도는 63.7-92.2%, 특이도는 81.0-94.9%로 보고되고 있다.[4,5] 또한 GE, Philips 및 Sienems 등의 주요 MRI 제조 업체들이 상업적인 지방량 측정 프로그램을 개발한 상태로 임상적용이 이전에 비하여 보다 쉬워졌다. 그러나 여전히 고가의 장비를 이용하게 되어 일차의료기관에서 보편적으로 이용하기 어렵다는 단점과 비용이 많이 발생되어 실제 임상에서 적용하는데 어려움이 있다.

2. 비알코올지방간 질환의 진단 (혈청학적 방법)

혈청학적 방법을 이용하여 비알코올지방간 질환을 진단하고자 하는 방법은 크게 세가지로 나뉠 수 있다. 첫째, 지방간(steatosis) 유무를 예측하고자 하는 검사와, 둘째, 지방간염(NASH)의 여부를 판단하고자 하는 방법, 그리고 마지막으로 진행된 간섬유화(advanced fibrosis, ≥ F3) 유무를 판단하고자 하는 검사 또는 생화학적 패널이 존재한다.

2.1. 단순지방간(simple steatosis)

우선 단순지방간(simple steatosis) 유무를 예측하고자 하는 검사 방법으로는 Fatty liver index, SteatoTest, NAFLD fatty liver score, Lipid accumulation product 등이 개발되었으나 임상에서 널리 사용되지 않는다.

2.2. 지방간염(steatohepatitis, NASH)

지방간염(NASH)의 진단과 관련되어 가장 많이 연구된 것은 CK-18이다. 간세포의 세포자살(apoptosis)을 나타내는 혈장 cytokeratin-18 (CK18) 분절(fragments)은 비알코올지방간염을 나타내는 표지자로서, 정상 또는 단순지방간 환자와 비교했을 때 지방간염환자에서 유의하게 증가 되어있으며, 일부 선행연구에서 비교적 좋은 결과(민감도78%, 특이도 87%, AUROC 0.82)를 보여, 비알코올지방간염에 대한 선별검사로서의 가능성을 보여주었다. 그러나, 그러나 CK-18의 임상적용의 가장 큰 문제점은 선행연구에서 제시된 기준치(cut-off value)가 연구자마다 매우 큰 차이를 보인다는 점이며, 두 번째로 지방간염을 예측하는 민감도와 특이도가 다소 떨어진다는 점이다.[6] 최근 11개의 연구를 이용한 메타 분석에서 비알코올지방간염의 CK-18의 기준치를 130-338 U/L로 하였을 때 Areas under the receiver-operating curve (AUROC)는 0.71-0.93 이였으며, 민감도는 약 66%, 특이도는 82%였다. 이러한 이유로 아직 우리나라를 비롯하여 미국간학회에서 비 알코올 지방간의 진단 및 치료를 위하여 일반적으로CK-18의 검사를 일반적으로 권고하고 있지 않다. 지방간염(NASH)을 예측하는 생화학적 패널 검사들로는 Nashtest, NASH diagnostic, NASH model, Nice model, HAIR score 등이 제시되었으나 보다 많은 추가 연구를 통하여 검증이 필요하다고 하겠다.

2.3. 간내 진행된 섬유화(advanced fibrosis, ≥ F3)

간내 진행된 섬유화(advanced fibrosis, ≥ F3)를 예측하기 위하여 AAR, APRI, BAAT, BARD, FIB-4, Fibrotest, NAFLD fibrosis score 및 ELF score 등이 이용된다. 이중 NAFLD Fibrosis Score (NFS)가 가장 많이 연구되었다. 임상적 또는 생화학적으로 쉽게 측정되는 6개의 표지자로 구성되어 있다는 장점이 있다. NAFLD fibrosis score는 특징적으로 low cut off value와 high cut off value 를 사용하며 low cut off 으로 하는 경우는 (-1.455) F3 진행된 섬유화를 예측하는 NPV가 93% 였으며, high cut off의 경우 (0.676) F3 이상의 양성 예측율이 90% 였다.[7] 이후 NAFLD fibrosis score는 다른 서양 국가에서 external validation이 되었으며 비교적 다른 섬유화 예측 모델과 비교하여 좋은 예측능력을 보여 주었다. 기존의 동양에서 이루어진 NAFLD fibrosis score을 이용한 external validation 연구의 결과를 보면 high cut off의 양성 예측율이 0-43%로 매우 낮다. 홍콩에서 162명의 NAFLD 환자를 대상으로 시행한 연구에서, low cut off value에 해당되는 경우는 NPV는 91%로 매우 우수하였으나 high cut off value를 보이는 사람에서 PPV는 0% 였다.[8] 홍콩 코호트의 경우 대상자의 평균 BMI는 28.5로 비만하였으나 F3 이상의 진행된 섬유화는 18명(11%)였다. 일본의 8개의 다기관 연구 588명을 대상으로 한 연구에서 low cut off에서 NPV는 98%, high cut off 에서 PPV는 43%를 보였다. 일본 코호트의 경우 27.8%가 F3이상의 진행된 섬유화를 보였다. 한국에서 검진 코호트를 이용하여 NAFLD fibrosis score의 external validation 연구에서 F3 이상의 진행된 섬유화를 예측하는 능력은 AUROC는 0.964로 매우 높았다.[9] 그러나 NAFLD fibrosis score의 low cut off을 이용한 NPV는 100%으로 높았으나, high cut off에서 PPV는 33.3%였다. 남미(멕시코, 칠레)의 228명의 환자를 대상으로 한 연구에서 F3 이상의 진행된 섬유화는 27명 (11.8%) 였다.[10] 그러므로 진행된 섬유화 비율이 낮은 동양권에서 high cut off를 이용한 PPV 의 사용에 대하여서는 보다 면밀한 판단이 필요하다.

3. 비알코올지방간 질환의 진단 (조직생검)

현재까지 비알코올지방간 질환의 진단은 조직검사이다. 그러나 조직생검을 통한 비알코올지방간 진단은 아래와 같은 해결되지 않은 문제가 있어, '완벽한(perfect)' 검사라기 보다는 '최선(best)'의 방법이라고 할 수 있다.

조직생검과 관련되어 해결되지 않은 문제는 아래와 같다. 첫째, 진행된 비알코올지방간 연관 간경변증(NASH associated cirrhosis)의 경우 간내 지방이 모두 연소되어 지방이 없을 수 있다(burn out cirrhosis)는 점이다. 이런 경우 원인미상의 간경변(cryptogenic cirrhosis)와 감별이 매우 어렵다. 술의 마시지 않는 환자에서 perisinusoidal fibrosis, ballooning hepatocyte, Mallory-Denk body가 관찰된다면 비알코올지방간 연관 간경변증(NASH associated cirrhosis)을 의심할 수 있는 단서가 되겠지만, 이전에 조직생검을 통하여 지방간염(NASH)을 확인된 경우가 아니라면 'burned-out' cirrhosis와의 감별진단은 매우 어렵다.

둘째, 조직생검의 경우 전체 간의 매우 극소수의 부분을 이용하기 때문에, 조직생검의 위치와 방법에 따라 상이한 결과를 얻을 수 있다.

셋째, 간조직을 얻는 방법과 위치에 따라 검사 결과가 다르게 나올 수 있다. 실제 오른쪽과 왼쪽에서 시행된 간조직생검의 결과의 일치도는 낮으며, 세침을 이용한 조직생검(needle biopsy)와 수술에 의하여 얻어지는 조직생검의 결과는 다르다고 알려져 있다. 수술에 의하여 간조직을 얻는 경우 시행되는 마취 자체에 의하여 미세한 간염이 발생 할 수 있다고 알려져 있다. 이를 'surgical hepatitis'라고 부르기도 한다.[11] 또한 수술에 의하여 간조직을 얻는 경우 간의 중심부가 아닌 표면에서 얻어지는 경우가 많으며 표면에서 얻어지는 경우 문맥부분의 확장 및 섬유화 소견이 보다 과장되어 관찰되는 경우가 많다.

넷째, 조직생검 결과 해석에 있어 관찰자 간(inter-observer)의 그리고 관찰자 내(intra-observer)에서의 일치도가 낮은 경우가 있다.

마지막으로 지방간염(NASH)의 진단과 정도를 판단하는 진단기준이 제시되고 있으나 아직 통일된 진단기준이 정하여

지지 않았다는 점이 있다. 현재 임상에서 지방간염의 조직학적 진단을 위하여 세 개의 기준(Brunt system, NASH CRN, SAF/FLIP algorithm)이 많이 사용되고 있다. Brunt system의 경우 비알코올지방간 질환의 조직학적 진단기준의 원형이 된 기준이다. Brunt system은 지방증, 간세포의 풍선변성 및 소엽과 문맥의 염증을 세 부류(mild, moderate, severe)로 나누고, 간섬유화는 1-4 단계로 평가하였다.[12] 또한 간내 지방의 축적과 염증세포의 침윤 이외에 간세포의 풍선양 변화(ballooning)에 중요한 관심을 두었으며, 특히 zone 3에서의 손상에 중요성을 제시하였다. 그러나 아직 광범위하여 다른 연구자들에 의하여 validation이 되지 않았다는 단점이 있다. NAS는 미국의 clinical research network in non-alcoholic steatohepatitis (CRN)에 의하여 제시되었으며, 많은 연구자들에 의하여 임상적 유용성을 확인(validation) 하였다.[13] 그러나 NAS는 지방간염(NASH)를 진단하기 위하여 만들어진 것이 아니며, 지방간질환 약물 임상연구에서 약물의 효능을 평가하기 위하여 만들어진 방법으로 지방간염을 진단 하는데 문제가 있다. NAS 체계에서 섬유화를 판단하는 항목은 존재하나 NAS 점수에는 섬유화 여부가 포함되지 않는다. 이러한 이유로 하여 진행된 간내 섬유화를 동반하고 있으나 NAS 점수가 낮은 사람이 있으며 이와 반대가 되는 경우가 있을 수 있다. 연구에서 명백한 steatohepatitis (NASH) 환자에서 28%는 NAS 점수가 5점 미만 이였으며, 명백하게 지방간염이 아닌 환자에서 7%에서 반대로 NAS 점수가 5점 이상 이였다.[14] 최근 유럽 fatty liver inhibition of progression (FLIP) 그룹에서 SAF score를 제시하였다.[1516,] SAF는 Steathosis, Activity (inflammation), Fibrosis 를 함께 평가하였으며 NAS 점수체계와 달리 간내 섬유화와 간세포의 풍선양 변화(ballooning)에 가중치를 두어 NASH를 진단할 수 있도록 하였다. SAF 장점은 관찰자간의 차이가 보다 적다는 장점도 가지고 있다. 향후 다양한 진단기준 및 중등도의 평가 방법에 대하여 보다 체계적인 합의가 필요하다고 하겠다.

조직생검은 상기의 여러 가지 문제점이 제기되고 있으나 그러나 아직 비알코올지방간 질환을 진단하고 치료효과를 판정하는데 현실과 임상에서 gold standard로 인정받고 있다. 향후 조직학적 진단과 관련되어 가장 큰 이슈는 세계적으로 일치된 조직학적 진단기준의 제시와 이를 판독하는 관찰자간의 일치도를 높일 수 있는 방안의 제시, 그리고 조직생검의 위치 및 방법을 표준화 하는 일이라고 할 수 있다.

4. 비알코올지방간 질환의 치료

4.1 식이습관 조절

비알코올지방간 질환의 치료 근간은 식이 및 운동습관 교정을 통한 체중감소이다. 최소 5%의 체중감소는 간내 지방량을 감소시킨다고 알려져 있으며, 간내 염증의 호전을 위하여서는 7-10%의 체중 감량이 필요하다고 보고되고 있다.[17,18] 그러나 현실에서 지속적인 체중감량을 위한 식이 및 운동 치료가 어려우며, 10%의 체중 감량을 지속적으로 유지하기도 어렵다.

최근 쿠바에서 시행된 저칼로리 식이 및 생활습관 교정 연구에서 1년동안 30%의 대상자가 체중감량이 이루어졌다.[19] 그러나 간내 섬유화 개선이 이루어진 경우는 19%에 불과하였으며, 이중 16%는 오히려 간내 섬유화가 진행되었다. 이전에는 유산소 운동이 저항운동(근력운동) 보다 간내 지방량을 감소하는데 유리하다고 하였으나, 최근 연구에서는 유산소 운동과 저항운동 함께 진행하는 경우 유산소 운동만 하는 것 보다 효과적이라고 보고되었다.

4.2. 약물 요법

비알코올지방간 질환에서 여러 개의 무작위 대조군 임상연구에서 효과가 입증된 약물이 몇 개 있으나 아직 대부분의 나라에서 비알코올지방간 질환의 치료제로 당국으로부터 허가를 받은 약물은 없다.

Obeticholic acid의 경우 FXR의 작용물질(agonist)로 지방간 환자에서 간내 염증을 의미 있게 감소시켰다.[20] 그러나 obeticholic acid는 동시에 혈중 중성지방 및 저밀도 콜레스테롤(LDL-cholesterol)의 수치도 의미 있게 상승시켰으며, 혈중 고밀도 콜레스테롤(HDL-cholesterol)의 농도도 감소 시켰다. 최근에 다른 종류의 FXR 길항제(agonist)인 intestinal

specific FXR agonist 를 이용한 연구에서 장특이적인(intestinal specific) FXR agonist는 지방세포 주변의 염증세포 침윤의 감소 및 인슐린 저항성을 개선시켰으며, 간내 지방의 양과 염증을 감소 시켰다. 흥미로운 점은 intestinal specific FXR agonist의 경우 콜레스테롤과 중성지방의 농도를 높이지 않았다.[21] 그러나 향후 사람을 대상으로 하는 연구가 필요한 상태이다.

NOX-1 and NOX-4 inhibitor (GKT137831)의 경우 NOX 1 and 4 을 타깃으로 하는 first in class 약물이다. NOX는 염증세포 및 간성상세포에 존재 하면서 간내 염증의 생성과 간내 섬유화 발생에 중요한 역할을 하는 물질이다. 동물실험에서 NOX1/4 억제는 간내 염증과 섬유화 억제에 우수한 효과를 보였으며,[22] 향후 임상시험 결과를 기다리고 있다.

Galectin-3는 glycoprotein 등과 같이 큰 단백질의 갈락토스 잔여기에 결합하는 탄수화물 결합 단백질의 일종이다. Galectin-3 은 면역세포에 정상적인 경우 매우 낮은 농도로 발현을 하고 있으나 염증이 발생되는 경우에 매우 높은 농도로 증가하게 된다.[23] Galectin-3길항제(antagonist)는 현재까지 동물 실험에 우수한 결과를 보여주고 있다. Galectin-3가 없는 결핍 마우스에서 간내 섬유화의 발생이 억제되었다. GR-MD-02 (Galectin Therapeutics, Inc, Norcross, GA, USA)는 아직 정확한 작용 기전이 규명되지 않았으나 galectin에 길항제로 작용을 할 것으로 예상되고 있다. 현재 GR-MD-02 는 phase II 에서 안전성과 효능 평가 임상시험을 진행하고 있으며 결과를 기대하고 있다(ClinicalTrial.gov NCT02462967).

Cenicriviroc (CVC)는 CCR2와 CCR5의 길항제이다. CCR은 chemokine receptor로 단핵구, 대식세포 및 간의 쿠퍼세포 등의 다양한 면역세포에 발현을 한다. 또한 CCR은 간성상세포의 활성화에도 중요한 역할을 하여 간내 섬유화에도 중요한 역할을 한다고 알려져 있다.[24] 현재 CVC을 이용한 CENTAUR 임상연구가 비알코올 지방간 환자를 대상으로 진행중에 있으며,[24] CVC의 안전성 및 효과에 대한 결과를 기다리고 있다(ClinicalTrial.gov NCT02217475).

Emricasan (Conatus Pharmaceuticals, Inc., San Diego, CA, USA)은 pancaspase 저해제이다. 이미 apoptosis는 비알코올 지방간질환에 매우 중요한 병태생리로 주목을 받아 왔으며, 비알코올지방간염의 진단에 있어 가장 중요한 간세포의 풍선양변화(hepatocyte ballooning)은 간세포의 사멸의 마커로 인식되어 왔다. 이미 다른 다양한 pancaspase inhibitor를 이용한 전임상 및 임상결과에서 비알코올지방간 질환에 매우 좋은 결과를 보여주었다.[25] Emricasan은 38명의 지방간염 환자를 대상으로 phase II 임상연구에서 혈청 ALT 및 cleaved CK18의 혈청 농도를 감소시켜 주었다.

GFT505 (Genfit, Loos, France)는 PPAR-alpha/delta agonist로 개발되었다. 이미 PPAR-alpha의 경우 간내지방을 감소시고 염증을 완화하는 작용이 있다고 알려져 있다. 그러나 아직 PPAR-delta의 역할에 대하여는 알려진 바가 적으나 PPARδ 는 사립체(mitochondria)의 기능을 향상시키고 지방의 연소를 촉진하고 인슐린 저항성을 개선시키는 효과가 있다고 알려져 있다. 274명의 지방간 환자를 이용한 대규모 무작위 대조군 연구에서 GFT505의 투여는 간내 염증호전을 의미 있게 감소시키지 못 하였다(초록 발표). 그러나 subgroup 분석에서 치료 시작전 NAS 점수가 4점 이상인 경우 GFT505의 투여는 의미 있는 간내 염증 호전을 유도하였다. 현재 GFT505의 임상적용 최적화를 위한 타깃 대상군 및 적정 투여시기에 대한 추가적인 연구가 진행 중에 있다.

Aramchol (Trima Israel Pharmaceutical Products Ltd., Maabarot, Israel)은 SCD-1 저해제로 SCD-1은 중성지방 합성에 중요한 효소로 중성지방의 생합성 억제에 매우 강력한 효과를 보인다. Aramchol은 60명의 조직생검으로 지방간으로 확진된 환자를 대상으로 3개월간 투여한 연구에서 의미 있는 간내 지방량의 감소를 보였다(초록발표). 그러나 상기의 연구에서 지방간염 환자는 6명(10%)에 불과하였으며 간내 섬유화 감소에 대한 연구결과는 포함되지 않았다. 현재 Aramchol은 240명의 지방간 환자를 대상으로 phase IIb 임상을 진행하고 있으며 이 연구에서는 간내 염증 뿐 아니라 간내 섬유화 정도를 비침습적으로 판단할 수 있는 지표를 이용하였다(ClincialTrails.gov NCT02279524).

ASK1은 apoptosis signal regulating kinase 1으로 체내에서 고혈당, TGF-β, 및 산화자극 등 다양한 자극에 의하여 활성화 된다. ASK1의 활성화는 p38과 JNK1 경로를 통하여 세포의 사멸과 섬유화를 유도한다고 알려져 있다. 동물 지방간염 모델에서 ASK1 길항제는 간내 지방량의 감소 및 간내 섬유화 감소를 유도하였다. 또한 ASK1 길항제는 체중 감소를 유도하여 인슐린 저항성 개선 및 체내 대사지표의 개선을 유도하였다. 현재 ASK1 antagonist (GS-4997)은

phase II 임상을 진행 중에 있으며 중등도의 지방간과 진행된 섬유화를 동반한 지방간염 환자를 대상으로 결과를 기다리고 있다(ClinicalTrial.gov NCT02466516).

Lysyk oxidase-like 2 (LOXL2)는 세포외 기질에서 콜라젠의 결합을 강화시켜, 분해를 억제하는 역할을 한다. 간경변 모델에서 LOXL2의 발현은 증가 한다. 동물 모델에서 LOXL2 단일 항체는 간내 섬유화를 억제하였다.[26] Simtuzumab (Gilead Sciences, Foster City, USA)은 현재 비알코올지방간 질환에서 간내 섬유화 진행 억제와 간경변 발생 억제에 대한 Phase IIb 연구를 진행 중이다. 상기 연구는 222명의 지방간염 환자를 대상으로 6년간 추적검사를 시행하여 간경변 발생에 대한 발생율을 함께 평가하고 있다(ClincialTrial.gov NCT01672866). 또한 동시에 지방간과 연관된 간경변 환자에서 simtuzumab의 안전성과 효과에 대한 Phase IIb 임상 연구를 진행 중에 있다(ClincalTrial.gov NCT01672879). 상기 연구는 대상성 간경변 환자를 대상으로 최대 6년간 simtuzumab을 투여하여 HVPG를 측정하여 치료 후 HVPG의 감소량과 함께 간병변 관련 합병증 발생율을 평가하고 있다. 연구는 2024년에 종료될 예정이다.

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Hepatitis C Virus: One Pill Is Enough for All Genotype

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C형간염: 모든 유전자형의 치료가 가능한 단일 약제

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With the introduction of the direct acting antiviral agents (DAA) for the treatment of chronic hepatitis C, many changes are taking place. Sustained virological response (SVR) has been reported as 58-86% in peg-interferon and ribavirin combination therapy for chronic hepatitis C patients, but SVR was improved by more than 90% as from the DAA is used. In Korea, several regimens are approved for genotype 1 and 2 chronic hepatitis C. In the near future, once-daily regimen for short period will provide high rates of SVR among both previously treated and untreated patients infected with HCV genotype 1, 2, 3, 4, 5, or 6, including those with compensated cirrhosis. It is need to understand how to use the currently approved DAA therapy which are treatment indication, treatment duration, drug-drug interactions and safety profile in clinical practice.

Keywords: Hepatitis C, Direct antiviral agents, Genotype

서론

과거 만성 C형간염에 대한 치료는 페그인터페론과 리바비린 병합치료가 사용되었다. 하지만, C형간염 바이러스(HCV)에 직접 작용하는 direct-acting antiviral agents (DAA)가 개발되고 C형간염에 유효한 치료요법으로 승인되면서 우리나라를 포함한 각국의 만성 C형간염 진료가이드라인에서는 DAA를 기반으로 하는 다양한 치료법을 제시하고 있다. 그러나, C형간염 바이러스의 유전자형, 과거 치료법에 실패 여부, 간경변증 유무 및 resistant associate variant (RAV) 존재 여부에 따라 사용할 수 있는 DAA의 종류 및 치료 기간에는 제한이 있다. 본고에서는 현재 사용 가능한 치료제들을 우선 알아보고, 가까운 장래에 사용될 수 있는 약제들을 소개하고자 한다.

본론

현재의 치료

유전자 1형

1. Daclatasvir와 Asunaprevir 병합요법

Daclatasvir (Daklinza®)는 NS5A 억제제로 60 mg 1정을 식사와 관계없이 하루에 한 번 투여하고, asunaprevir (Sunvepra®)는 NS3/4A protease inhibitor (PI)로 100 mg 1캡슐을 식사와 관계 없이 하루에 두 번 투여한다. Daclatasvir와 asunaprevir 병합요법의 치료 기간은 24주이다. Daclatasvir와 asunaprevir 병합요법은 유전자 1형 C형간염 중 유전자아형 1b형에서만 치료 효과가 입증되어 반드시 치료 시작 전 유전자형과 함께 유전자아형을 정확하게 판별할 수

있는 검사가 필요하다. 치료 경험이 없는 유전자형 1b형 C형간염 환자 205명을 대상으로 한 daclatasvir와 asunaprevir 24주 병합요법은 90% SVR률을 보였다.[1] 성별, 인종, IL28B 유전자 다형성, 간경변증 유무에 따른 SVR률의 차이는 없었다. 이전 치료 경험이 있는 440명의 유전자형 1b형 환자를 대상으로 한 daclatasvir와 asunaprevir 24주 병합요법에서 이전 치료에 무반응자, 인터페론 부적합/불내성 환자가 각각 82%와 82%의 SVR률을 보였다.[1] 일본에서 진행된 3상 연구에서는 이전 인터페론/리바비린 치료에 무반응을 보인 87명과 인터페론 부적합/불내성 환자 135명에서 daclatasvir와 asunaprevir 24주 병합요법으로 전체 85%(188/222)의 SVR률을 보였다.[2] 이전 치료에 무반응이었던 환자군에서는 SVR률 81%(70/87), 인터페론 부적합/불내성 환자군에서는 87%(118/135)였으며, 간경변증 유무와 상관없이 치료반응이 유사하였다. 치료 전 12.6%-14.4%의 환자들에서 NS5A 부위 (L31 또는 Y93)의 resistant associated variants (RAV)가 동반여부가 확인되었으며, 이 변이가 동반된 대상자의 경우 daclatasvir와 asunaprevir 24주 병합요법의 치료 결과는 낮게 보고되었다. Daclatasvir와 asunaprevir 병합 24주 요법으로 진행된 5개의 연구 통합분석 결과(치료 경험 환자 포함 총 979명)에서 치료 전 NS5A 부위의 L31 또는 Y93 코돈의 변이가 동반된 경우에는 SVR률(39%)이 낮았고, 해당 변이가 없는 경우 SVR률은 94%로 높았다.[3] 따라서, 치료 전 반드시 NS5A 내성 관련 변이 검사를 시행하고 변이가 검출될 경우에는 daclatasvir와 asunaprevir 병합요법은 권고되지 않는다. Daclatasvir와 asunaprevir 병합 24주 요법의 치료 중 부작용으로 인한 치료 중단은 1%였으며, 5%이상 빈발한 부작용에는 두통 (15%), 피로 (12%), 설사 (9%), 구역 (8%), ALT 상승 (7%) 등이 있었다.[1,2]

2. Ledipasvir/sofosbuvir 고정 용량 단일 정제

Ledipasvir/sofosbuvir (Harvoni®)는 NS5A 억제제인 ledipasvir 90 mg와 NS5B 뉴클레오시드 중합효소 억제제인 sofosbuvir 400 mg을 포함하는 고정 용량 단일 정제로 식사와 관계없이 경구로 하루에 한 번 투약한다. 투약 기간은 유전자 1형 만성 C형간염 환자에서 12주이나, 과거 치료 경험이 있는 대상성 간경변증 환자 및 비대상성 간경변증 (치료 경험 유무와 관계 없이)의 경우 리바비린을 추가하여 12주 투약하거나 ledipasvir/sofosbuvir 단독으로 24주 치료할 수 있다. 치료 시작 전 바이러스 농도, 연령, IL28B 유전자 다형성 등은 치료 반응에 유의한 영향을 주지 않으며, daclatasvir와 asunaprevir 병합치료와는 달리 치료 전 RVR 존재 여부 및 유전자아형 (1a 혹은 1b)에 따른 SVR률에 차이가 없어 치료 전 별도의 RAV 검사가 필요하지 않고, 유전자아형에 따른 치료 적용에도 차이가 없다. 치료 경험이 없는 유전자형 1형 환자 865명을 대상으로 ledipasvir/sofosbuvir 12주 치료를 시행하였을 때 SVR률은 99%였다. 리바비린을 추가하거나 치료 기간을 24주로 연장하여도 추가적인 이득은 없었다.[4] 16%의 환자에서는 치료 전 ledipasvir에 대한 RAV가 검출되었으나 RAV 존재 여부는 치료 결과에 유의한 영향을 주지 않았다.[5] 이전 치료 무반응환자 44%와 이전 PI 치료 실패 환자 53%가 포함된 440명에서 ledipasvir/sofosbuvir 12주 치료는 94%의 SVR률을 보여, ledipasvir/sofosbuvir와 리바비린 12주 병합요법(SVR률 96%) 및 ledipasvir/sofosbuvir 24주 치료(SVR률 99%)와 유의한 차이가 없었다.[6] 치료 시작 전 NS5A 억제제에 대한 RAV가 14%의 환자에서 발견되었으나, 이들 중 89%에서 치료 반응이 있었다.

국내에 시행된 연구 결과에서는 이전 치료 경험 환자를 포함한 93명 환자(초치료 46명, 이전 치료 실패 47명)에서 ledipasvir/sofosbuvir 12주 치료로 99%(92/93)의 SVR률을 보였고, 간경변증 환자에서도 100%의 SVR률(17/17)을 보였다. 치료 시작 전 22%의 환자에서 NS5A 억제제에 대한 RAV가 있었으나, 이 중 95%에서 치료반응을 보였다.[7] Ledipasvir/sofosbuvir의 12주 또는 24주 치료 중 5%이상 빈발한 부작용에는 피로 (13-18%), 두통 (14-17%), 구역 (7-9%), 설사 (3-7%), 불면 (5-6%) 등이 있었다.[4]

유전자 2형

1. Sofosbuvir와 Ribavirin 병합요법

Sofosbuvir (Sovaldi®) 400 mg과 체중에 따라 조절된 ribavirin (체중 ≥75 kg이면 1,200 mg, 체중 < 75 kg이면 1,000 mg)을 병합하여 12주간 매일 경구 투여한다. 국내 환자 129명을 대상으로 한 3상 연구에서 sofosbuvir와 리바비린의 12주 병합요법 SVR률은 97% 이었다.[8] 국내 연구에서는 sofosbuvir와 리바비린 12주 치료로 간경변증 환자의 SVR률

이 100% 였으나 참여한 환자 수가 13명으로 많지 않았다.[8] Sofosbuvir와 리바비린 12주 병합요법에 대한 FISSION 연구에서 SVR률에 영향을 미치는 요인으로 간경변증이 있었고,[9] 간경변증이 SVR 달성을 방해하는 인자임을 고려할 때, 간경변증이 동반된 유전자형 2형 환자에서는 sofosbuvir와 리바비린 병합요법 치료 기간을 16주로 늘리는 것이 추천된다.

향후의 치료

1. Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir (Epiclusa®)는 sofosubuvir 400 mg에 NS5A 억제제인 velpatasvir 100 mg을 포함한 단일 정제로 하루 한 번 복용하는 약제이다. DAA의 치료효과에 영향을 미치는 치료 경험 유무, 간경변증 유무에 관계없이 12주 치료에 99%의 SVR률을 보였다.[10, 11] 특히, 모든 유전자형에서 높은 SVR률 (ASTRAL-1 연구: 유전자 1a형 98%, 유전자 1b형 99%, 유전자 2형 100%, 유전자 4형 100%, 유전자 5형 97%, 유전자 6형 100% / ASTRAL-2 연구: 유전자 2형 99%, 유전자 3형 95%)을 보였다. 치료 전 NS5A 부위(Q30R) 및 NS5B 부위(S282)에서 RAV가 발견되나, RAV를 가진 환자에서도 99-100%의 SVR률을 보였다. 가장 흔한 이상반응으로는 피로, 두통, 구역, 불면증 등이었다.

2. Sofosbuvir/velpatasvir와 GS-9857 병합요법

Sofosbuvir/velpatasvir 단일 정제와 NS3/4A protease inhibitor인 GS-9857 100mg 을 12주간 경구로 하루에 한 번 투약한다. 이전 DAA 치료에 실패하였던 유전자 1-6형 환자를 대상으로 12주 투약한 연구에서 높은 SVR률 (유전자 1형 100%, 유전자 2, 4-6형, 100%, 유전자 3형 97%)을 보였다. 가장 흔한 이상반응으로는 두통, 피로, 설사. 구역 등이었다.

결론

최근 만성 C형간염의 치료는 빠른 속도로 발전하고 있으며, 향후 경구 항바이러스제의 역할은 점차 확대될 것으로 생각된다. 현재 국내에서 이미 승인된 약제 및 치료법 이외에도 다양한 치료제가 계속 개발되고 있으며, 향후에는 C형간염 바이러스의 유전자형, 과거 치료법에 실패 여부, 간경변증 유무 및 RAV의 존재 여부와 상관없이 단기간에 최소한의 부작용으로 높은 치료 효과를 달성하는 치료제가 도입될 것이다. 다만, 새로운 약제의 우수한 효과와 안전성이 입증되어도 높은 비용 등으로 인해 국내에서는 사용 허가 및 의료보험 적용이 선별적으로 적용될 수 있다. 임상의사는 현재 사용 가능한 치료제들의 정확한 치료법을 이해해야 하겠으며, 가까운 장래에 사용될 수 있는 약제들의 임상적 유용성을 함께 고려하여 환자의 특성과 상황에 맞는 최적의 치료 시기와 방법을 선택해야 하겠다.

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Hepatitis B Virus: Changing Antiviral Treatment Strategies: Low Viral Load in Liver Cirrhosis with Hepatitis B Virus

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B형간염 바이러스: 변화하는 항바이러스 치료 전략: 간경변 동반된 낮은 바이러스 혈중 농도를 보이는 환자

신 동 현

성균관대학교 삼성서울병원 내과

Unfortunately, there are no effective cures for hepatitis B virus (HBV); currently available treatments, such as interferons and nucleoside/nucleotide analogues (NUCs), can suppress viral replication but cannot eradicate the virus. Therefore, decision to treat should be individualized based on balancing the risk (i.e., un-treated natural course, side effects from treatments, cost) and benefit of the treatment. Generally, patients with low viral load (< 2,000 IU/mL) are considered as a group at low risk for developing hepatic complications. Therefore treatment are usually recommended for those who shows elevated HBV DNA levels (≥ 2,000 IU/mL). Yet, recent studies suggest treatment strategy should also consider the severity of liver disease. Herein, we will discuss recent evidences for the risk and benefit of antiviral therapy in cirrhotic patients who shows low level viremia.

B형간염은 국내에서 진단되는 간암 및 간경변의 가장 중요한 원인이다.[1] B형간염의 예후는 바이러스 증식과 매우 밀접한 연관이 있으며, 바이러스 증식정도는 간암 및 간경변 합병증의 발생과도 연관되어 있다.[1] 다행히 B형간염의 증식을 효과적으로 억제할 수 있는 다양한 약제들이 개발되어 임상에서 널리 활용되고 있으며, 최근에는 거의 대부분의 환자들에서 B형간염의 증식을 효과적으로 억제할 수 있다.[2] 효과적인 바이러스 증식 억제를 B형간염 환자들의 예후를 크게 개선할 수 있어, 치료성적이 매우 개선되었다. 가장 널리 활용되는 경구용 항바러스제들을 사용하게 되면, 혈중 B형간염 농도는 빠르게 감소하며, 간의 염증이 개선되며, 간섬유화 호전, 간암발생율 감소, 비대상성 간경변 발생 예방 및 비대상성 간경변 화자의 예후를 개선할 수 있다.[3-7] 과거에는 경구용 항바이러스 사용시 내성의 발생이 문제가 되었으나, 최근에 사용되는 강력한 바이러스 증식 억제제인 엔터카비어, 테노포비어와 같은 약제는 장기 사용에 따른 내성의 우려도 거의 없는 실정이다[8].

B형간염 환자의 자연경과를 보고한 대규모 연구인 REVEAL 연구에 의하면, 바이러스 증식 정도는 간암 등 합병증 발생과 매우 밀접한 연관이 있어, 혈중 바이러스 농도가 2000 IU/mL이하인 환자들의 간암 등 합병증 발생율은 매우 낮다고 보고하였다.[9] 따라서 혈중 바이러스 농도가 2000 IU/mL로 자연적으로 유지되는 환자들을 면역비활동기로 분류하며, 특별한 치료 없이 경과 관찰이 권유된다.[1] 그러나 이러한 권고안의 주요 근거는 간경변 증거가 없는 환자들에서 도출된 결과로, 일예로 REVEAL 연구에 참여한 환자들의 98%는 간경변의 증거가 없는 환자이었다.[9]

유럽간학회 및 미국간학회 진료 지침은 낮은 근거수준이나 혈청 HBV DNA농도가 2000 IU/mL이하라도 PCR검사 양성인 경우 간경변 환자들은 치료를 권고하고 있다.[10,11] 최근 개정된 대한간학회 진료지침에서도 낮은 근거수준이나 대상성 간경변증 환자들은 혈청 HBV DNA농도가 2000 IU/mL이하라도 PCR검사 양성인 경우 AST/ALT와 관계없이 치료를 고려할 수 있다고 권고하고 있다.[1] 여기서는 이러한 권고안의 이유들을 살펴보고자 한다.

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DAY 2: Friday, June 17, 2016 (16:30-18:10) WEST TOWER Room AB

Special Interest Group Symposium 1

Nonalcoholic Fatty Liver Disease (NAFLD): Non-obese NAFLD Patients

Chairs : Kwon Yoo (Ewha Womans Univ.)
So-Young Jin (Soonchunhyang Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Difference between Western and Eastern NAFLD Patients -Relationship to obesity and the importance of NAFLD biomarkers

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Recent changes in life style have given a big problem, obesity to human being, which is unexpected before 21st century. Numbers of patients with NAFLD (non-alcoholic fatty liver disease) are increasing in many countries. While NAFLD is associated with obesity, the correlation is a little different in each country, which might be dependent on genetic and/or environmental factors. In this symposium, I summarize a difference of obesity and NAFLD in each country and show the importance of biomarker for NAFLD/NASH to prevent HCC. Furthermore, I refer to talk about fucosylated AFP (AFP-L3) as a representative glyco-cancer biomarker for hepatocellular carcinoma.

Clinical Differences between Obese and Non-obese NAFLD Patients

Sang Hoon Park

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Pathogenesis of non-obese NAFLD

Non-alcoholic fatty liver disease (NAFLD) in the absence of obesity defined by body mass index (BMI) has been designated 'non-obese NAFLD'. The pathogenesis of 'classical non-alcoholic fatty liver disease (NAFLD)' is associated with metabolic syndromes such as type 2 diabetes (T2DM), hypertension and dyslipidemia.[1] Although Asians are less obese than Western people, the prevalence of NAFLD and metabolic syndrome is not lower than that Western people. Recently, several studies have shown that the prevalence of NAFLD in non-obese (BMI ≤ 25.0 kg/m2) population was 12.6-16.1% in Korea, 18.4% in Japan, and 7.2% in China.[2-5]

BMI is the most simple and commonly used measure of total body adiposity in clinical as well as epidemiological studies. Even though, BMI is regarded as a surrogate of body fat content, it is not stands for adiposity among different body compartments such as adipose tissue, skeletal muscle, and osseous elements.[6] Waist circumference (WC) and waist to hip ratio (WHR) is very useful as measures of central obesity (VAT) and also correlate more precisely with intra-abdominal fat.[7] In particular, Asians show a high prevalence of abdominal obesity reflected in higher waist to hip ratios (WHRs) and high truncal deep subcutaneous fat, even when they have normal BMIs.[8,9] Apart from total body adiposity, the distribution of fat in different body compartments have assumed greater relevance in pathophysiology of non-obese NAFLD. An increased fat mass in the visceral adipose tissue (VAT) makes non-obese subjects more susceptible to NAFLD, compared to increased subcutaneous fat in the BMI in healthy Asians.[10]

Recent research has shown that the size of adipocyte and their biological behavior are critical issues in the pathogenesis of metabolic syndrome.[11] There is inter-individual variation in adipocyte size between non-obese and obese people. The large adipocytes have markedly higher gene expression than small adipocytes. The majority of these genes were immune related, maintenance and regulation of cell structure.[12] Asians have been shown to have larger adipocytes compared to Caucasians and other ethnic groups.[13] Adipocyte turnover studies indicate that the overall size of adipocyte mass is set at a higher level of equilibrium in childhood and adolescence in obese, while adipocyte turnover in adulthood similar to that in non-obese adults.[11] In developing countries, nutritional stress is often in early life followed by relative abundance in adulthood. In contrast, the setting of developed countries where the age of switch to adipocyte mass expansion occurs in childhood and adolescence.[14] Thus, a relatively late trigger to adipocyte expansion may underlie the phenotypic differences between obese and non-obese NAFLD.[15]

Genetic factors as well as environmental factors are important in the development of NAFLD. Recent genome-side association studies (GWAS) have identified that single nucleotide polymorphism (SNP) in the patatin-like phospholipase domain containing 3 (PNPLA 3) were the most important genetic factor associated with NAFLD.[16,17] In different ethnic groups, it has been reported that the frequencies of the G-allele of rs738409 is 17% in African American, 23% in European descendants.[18,19] While its frequency is much higher in the Japanese than the other ethnic groups (45%). In a Japanese study showed that non-obese NAFLD subjects had a higher rs738409 GG genotype than obese NAFLD. And, G allele

of PNPLA3 rs738409 was associated lobular inflammation, hepatocyte ballooning and NAFLD activity score in non-obese NAFLD.[20] The other Japanese study showed that the G allele of PNPLA3 rs738409 is a prominent risk factor for NAFLD and the interaction between the PNPLA3 rs738409 and weight gain ≥ 10 kg after age 20 plays a crucial role in the pathogenesis of NAFLD, especially in non-obese individuals.[21]

Apart from genetics, dietary factors need to be elucidated in non-obese NAFLD. In a Japanese study suggests that NAFLD group had much greater carbohydrate intake than the control group and that the restriction of carbohydrates might contribute to the recovery of fatty liver.[22] East Asians (including Koreans) have a higher carbohydrate intake than white subjects, and high prevalence of non-obese NAFLD can be partially ascribed to the increased intake of higher percentage of carbohydrates in the regular diet.[3]

In addition to above pathophysiologic interplay, the distinct different compositions of gut microbes are reported between obese and non-obese NAFLD.[23]

Characteristics of non-obese and obese NAFLD

Studies on compared the clinical characteristics of the non-obese and obese NAFLD is very rare. A well-designed Japanese study reported that Non-obese NAFLD subjects had higher rs738409 GG genotype than obese (47.8% *vs*. 36.5%, P = 0.02), the number of female subjects were higher in non-obese than obese NAFLD and non-obese NAFLD patients were older than obese NAFLD patients.[24] While, as we thought other metabolic features and hepatic pathologies were somewhat bad in classical obese NAFLD. They performed multiple logistic regression analysis to investigate the effect of BMI, T2DM and rs738409 GG genotype on NAFLD with or without obesity adjusted for age and sex. The odd ratio of T2DM and rs738409 GG genotype were higher in non-obese than those in obese NAFLD (11.16 *vs*. 3.41; 4.15 *vs*. 2.76, respectively).[24]

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Genetic Aspects of Non-obese NAFLD Patients

Luca Valenti

Universita degli Studi di Milano, Italy

Epidemiological, familial, and twin studies indicate that non-alcoholic fatty liver disease (NAFLD), now the leading cause of liver damage in developed countries, has a strong heritability. The common I148M variant of Patatin-like phospholipase domain-containg-3 (PNPLA3) impairing hepatocellular lipid droplets remodeling is the major genetic determinant of hepatic fat content. The I148M variant has a strong impact on the full spectrum of liver damage related to fatty liver, encompassing non-alcoholic steatohepatitis, advanced fibrosis, and hepatocellular carcinoma, identifies a specific pathophysiological subtype of NAFLD, and influences the response to therapeutic approaches. Common variants in Glucokinase regulator (GCKR) also enhance de novo hepatic lipogenesis in response to glucose and liver inflammation. Furthermore, the E167K variant of Transmembrane-6 superfamily member-2 (TM6SF2) and the rs641738 non-coding polymorphism in the MBOAT7/TMC4 locus are associated with the development and progression of NAFLD, by altering lipidation of very-low density lipoproteins (VLDLs) and lipid secretion, and phosphatydil-inositol metabolism, respectively.

Genetic factors seem to contribute to an even greater extent to the pathogenesis of NAFLD in non-obese individuals, compensating for less severe metabolic cofactors that may be less important. For example, in some studies the PNPLA3 I148M variant has been reported to confer an even higher risk of disease than in obese subjects. Furthermore, rare mutations associated with severe loss-of-function of key proteins implicated in lipid metabolism are specifically associated with development of severe NAFLD in lean individuals. This is particularly true for mutations in Apolipoprotein B (APOB), which impair VLDLs secretion causing hepatocellular lipid retention and progressive liver disease, but at the same time may favor malnutrition by reducing fat absorption by enterocytes. Furthermore, mutations in lysosomal acid lipase (encoded by LIPA) may cause early onset progressive liver disease and atherosclerosis related to defective degradation of cholesterol and triglycerides in hepatocytes independently of insulin resistance.

These and other recent findings reviewed here indicate that impaired lipid handling by hepatocytes has a major role in the pathogenesis of NAFLD by triggering inflammation, fibrogenesis, and carcinogenesis. The role of the known genetic risk factors, and in particular those of rare variants with a strong phenotype, seems magnified in non-obese individuals, where metabolic determinants are less severe. These discoveries have provided potential novel biomarkers for clinical use, in particular for NAFLD typization in lean individuals, and have revealed intriguing therapeutic targets.

Therapeutic Approach in Non-obese NAFLD Patients

Jin-Woo Lee

Inha University, Korea

In East Asian countries, subjects with NAFLD are generally less obese than those in Western countries. A subset of individuals who are insulin resistant and have hyperinsulinemia, atherogenic lipid profiles, as well as hypertension, despite having normal BMIs, i.e., <25 kg/m^2. This group of individuals who are "metabolically obese normal weight (MONW)", which is possibly closely related to non-obese NASH. Non-obese subjects who gain weight despite being within the range of normal BMI or currently normal weight individuals who were obese in the past are found, so we need to consider BMI within a dynamic frame rather than as a single-point observation and strictly apply both BMI and WC criteria for the diagnosis of non-obese NASH. The distribution of fat in different body compartment may contribute to the development of insulin resistance in the "MONW" individuals in whom a sizable sum of fat content in the visceral adipose tissue (VAT) compartments is commonly observed.

Recent studies suggest that genetic predisposition along with nutritional status in childhood, dietary composition and gut microbiome also play a role in pathogenesis.

Metabolic abnormalities in non-obese NASH patients are similar to those seen in obese NASH, therefore standard diagnostic criteria and management strategy also seems to be applicable to non-obese subjects. Here we will provide insights to potential therapeutic approach in patients with non-obese NAFLD.

Behavioral therapy protocols for weight loss, the key stone of treatment in classical NASH. Although these therapeutic effects showed a decrease in the serum levels of aminotransferase and intrahepatic triglycerides in NAFLD, most of the studies were conducted in a general population or in overweight subjects. For that reason, there is still some dilemma in the management because it is unclear how the lifestyle modification would impact non-obese phenotype. In the absence of clear definition and definite pathogenic background for non-obese NASH, it would lead to somewhat wasteful exercise and expenditure especially in leaner population.

Treatments including thiazolidinediones, antioxidants like vitamin E, and statins only have a role in treatment of biopsy proven NASH irrespective of lean NASH or obese NASH. Emerging therapeutic targets such as those direct-acting by modifying insulin resistance, signaling of pathways of inflammation, and fibrosis as well as alterations in gut flora may find a core advantage.

Keywords: Non-alcoholic fatty liver disease (NAFLD), Non-obese NAFLD, Treatment

Hepatic Lipid and Glucose Metabolism in NAFLD

Douglas G. Mashek

Department of Biochemistry, Molecular Biology and Biophysics and Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, University of Minnesota, Minneapolis, MN, USA

Although defined by lipid accumulation, non-alcoholic fatty liver disease (NAFLD) exhibits alterations in both lipid and glucose metabolism. Alterations in hepatic lipid metabolism play an active role in the development of insulin resistance and associated increases in hepatic glucose production and hyperglycemia. While intermediates in triacylglycerol synthesis are thought to directly impair insulin signaling, there is also a growing body of literature suggesting that enhanced hepatic lipid catabolism may also regulate glucose production. Additionally, selective insulin resistance in the liver allows intact insulin-mediated regulation of lipid synthesis, but attenuates the ability of insulin to suppress hepatic glucose production. This presentation will discuss our current state of knowledge into the major factors regulating hepatic lipid and carbohydrate metabolism and, importantly, possible mechanisms linking these processes to NAFLD and related comorbidities. In particular, recent data will be presented that show the importance of hepatic lipolysis as an important regulator of liver signaling and glucose production.

DAY 2: Friday, June 17, 2016 (08:30-09:50) EAST TOWER Room A

KLTS Symposium 1

How to Minimize Living Donor's Damage and Maximize Living Donor's Safety?

Chairs : Hee-Jung Wang (Ajou Univ.)
Soon Il Kim (Yonsei Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Intra-operative Management for Donor Safety during Laparoscopic Donor Hepatectomy

Choon Hyuck David Kwon

Department of Surgery, Samsung Medical Center, Sungkyunkwan University, Korea

Laparoscopic hepatectomy has been shown to improve the postoperative recovery compared to open hepatectomy. However, laparoscopic hepatectomy requires a double expertise in the field of laparoscopy and HBP surgery and neither can be compromised to yield the best outcome of the patients. Donor hepatectomy for living donor liver transplantation requires optimal care since no unexpected mishaps is allowed during this technically challenging operation due to the safety of the donor which must be considered as the most important factor to consider. Therefore, laparoscopic donor hepatectomy requires a very well planned prudent approach for optimal outcome and safety of the donor.

There are several dangerous pitfalls during laparoscopic donor hepatectomy that should be taken into consideration.

1. Bleeding during parenchymal transection

The middle hepatic vein and its tributaries are found along the plane of parenchymal dissection during a right, right extended, left or left extended hepatectomy. The surgeon must know how to deal when unexpected bleeding occurs. Hemostatic agents (Surgicell®, Fibrillar®) and/or conventional gauze with or without increased intraabdominal pressure is a useful method to reduce bleeding from minor branches. Bipolar or advanced bipolar electrocautery device is also useful in controlling minor bleeding and keep the transection plane clear from oozing and blood. It is imperative for the surgeon to have a full knowledge of the anatomy of the tributaries in order to prevent tearing vein branches.

2. Bile duct division

Division of bile duct is one of the most crucial and challenging step during donor hepatectomy. Intraoperative cholangiogram with radiopaque tags or metal clips to verify the exact plane of division may be very helpful. Fluorescent image using indocyanine green dye is another option to improve the accuracy of division plane. If the Glissonean sheath surrounding the bile duct is left intact, bleeding is often encountered so control of incoming vessels, either using bulldog clamp or clips, may be useful

3. Portal vein division

The commercially available one side TAE often used for stapling the remnant portal vein has 3 stapling lines and is thus quite thick. The surgeon should be careful not to staple to close to the remnant portal vein since it may cause stricture. It is also recommended to expose the whole bifurcation of the portal vein in order to verify that the remnant portal vein won't be strictured after stapling.

4. Hepatic artery division

Two clips and/or Hem-o-lok® is often necessary to provide secure control of the artery. Moreover, dividing the artery too close to the clips should not be done and a margin of end stump should be left since slipping of the clip may occur resulting in arterial bleeding after or during the operation.

5. Mobilization of the liver

Division of the coronary ligament and the right triangular ligament may be done before or after the parenchymal division but dissecting the ligaments beforehand is recommended. Mishaps may occur during parenchymal division requiring prompt extraction of the graft and prior division will provide a shorter warm ischemic time. It is also important not to try to dissect to close to the IVC because the angle of approach is not easy during the early phase of surgery and dissection along the IVC may be done much easier from the medial side after completing parenchymal division.

6. Pfannentiel incision

The skin incision should be done before dividing the artery and portal vein in order to reduce the warm ischemic time.

Laparoscopic donor hepatectomy is not only one of the most technically challenging procedure but extra caution should be taken not to jeopardize the safety of the donor. Patients with anatomic variations may be difficult to operate and should not be considered as candidates of donor until otherwise proven to be safe. Patient safety should always be of first priority during laparoscopic donor hepatectomy just like in open donor hepatectomy and surgical mastery in both living donor hepatectomy and major laparoscopic hepatectomy should be acquired before starting a laparoscopic donor hepatectomy program.[1]

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Early Experience of Robotic Donor Hepatectomy: Learn from Pioneer

Gi Hong Choi

Division of HPB Surgery, Department of Surgery, Yonsei University College of Medicine, Korea

Living donor right hepatectomy is one of the complex liver resections because it requires the meticulous dissection of the liver hilum and the preservation of V5 and V8. Laparoscopic donor right hepatectomy has been performed in a few centers by expert surgeons. However, it is still a challenging procedure to many donor surgeons. Compared to laparoscopic hepatectomy, the advantages of robotic hepatectomy are maximized in the meticulous dissection of the liver hilum, the posterior side of the right liver and the inferior vena cava. As for parenchymal transection, robotic surgery has some limitations because of limited available instruments for parenchymal transection and no well-established transection technique.

From December 2008 to May 2016, 69 patients underwent robotic liver resection using the da Vinci Surgical System® (Intuitive Surgical, Sunnyvale, CA) in our institute by single surgeon. From the caudate lobe (S1) to segment 8, almost all types of liver resection have been performed, including 54 major hepatectomy. During this experience, we have established unique techniques for parenchymal transection, which are the rubber band traction method to make stable traction of parenchymal transection plane and the parenchymal transection using Harmonic scalpel and Maryland bipolar forceps. Until now, two living donor right hepatectomies have been performed using robotic systems in our institute. Tow donors and recipients were discharged without any significant complications.at postoperative days 9 and 21, respectively.

From our early experience, robotic living donor right hepatectomy is feasible. The more detailed procedures have to be standardized in the division and repair of the right bile duct and parenchymal transection. The utility of ICG fluorescence image should be explored in robotic living donor hepatectomy.

Post-donated Complications after Donor Hepatectomy: Achilles Heel of Donor Surgeon

Young Seok Han

Kyungpook National University School of Medicine, Kyungpook National University Hospital

Since living donor liver transplantation (LDLT) was introduced, the LDLT procedure has been accepted because of organ shortage from deceased donors. In particular, LDLT is the main treatment option of end-staged liver disease in Korea. The chief concern of LDLT as described "Achilles Heel" must be donor safety. Exposure of healthy donor candidates to major surgery which can be fatal is the largest of these ethical problems. And, complete prevention of donor complication is not always feasible. Since the adoption of the right lobe liver for LDLT, more concerns about a perfectly healthy donor receiving a major hepatectomy have emerged. The various critical analysis of surgical outcomes would suggest that reported morbidity rates are characteristically underestimated. Nevertheless, according to recent reports, the average prevalence of mortality and morbidity are 0.2% and 24%, respectively, in spite of surgical refinements and innovations as well as better preoperative and postoperative management for donor hepatectomy.

The main factors responsible for loss of the donor are sepsis and liver failure. The small volume of the remaining remnant liver, excessive intraoperative blood loss, and intraoperative anesthetic management were responsible for liver failure after donor hepatectomy.

The most frequently encountered complications are pleural effusion, bile leakage and wound infection, but usually medical interventions are not required. According to the reports of centers in the United States, Japan, and Korea, the most common problem after right lobe donor hepatectomy is biliary tract complication. The incidence of bile leaks and bile duct strictures requiring treatment is approximately 4%. To minimize injury to the bile duct, we have to not to leave any segment of the liver undrained, to avoid cautery as much as possible in the hilar plate, to reveal the intrahepatic bile duct with intraoperative cholangiography, and to close the residual biliary limp carefully.

Intraoperative and postoperative bleeding is another common causes of liver morbidity. Hence, donor hepatectomy requires greater care and enough experiences of hepatectomy for hepatobiliary disease.

Minimally invasive liver surgery has many advantages over the conventional open surgery. The permanent large abdominal incision scar following conventional open surgery may cause some living donors, especially young women, mental and physical stress, leading to hesitation with undergoing donor hepatectomy. However, laparoscopic or robotic surgery don't have to be extended to a living donor candidate without sufficient concerns for donor safety. The aim of laparoscopic approach for living liver donor is not with aesthetic result or less pain but with a decrease in the rate of complications.

In summary, because donor safety is of paramount significant, further innovative surgical techniques and perioperative management are required and the established criteria for graft selection should be upgraded. And, we should make greater efforts to complete prevention of donor complications.

Fate of Live Donor after Liver Donation: Physician's View

Dong Hyun Sinn

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생존간기증: 내과 의사의 견해

신 동 현

성균관대학교 삼성서울병원 내과

Liver transplantation saves life and is sometime the only option for the patients suffering from various liver disease. The organ shortage has encouraged the development of living liver donation, and provides the only realistic chance of survival in some cases. However, living donation is not complication-free in donors. Herein, we will discuss evaluation process in living donor evaluation and long-term health outcome of donor, to seek a way to minimize living donor's damage and maximize living donor's safety.

간이식은 환자의 간을 사망한 사람의 간 전부나 일부, 혹은 살아있는 사람의 간 일부로 대체하는 것을 말한다. 간이식은 간질환을 근본적으로 교정할 수 있는 장점이 있으며, 간질환의 주요 치료법이다. 뇌사 기증자는 간이식 희망자에 비해 매우 부족하여, 뇌사 기증자의 부족을 보완하는 방법으로 살아있는 사람의 간 일부분만 사용하여 기증하는 형태를 생체 간이식이라고 한다. 현재 우리나라는 간이식 대기자 10명 중 1명 정도만이 1년 내에 뇌사자 장기를 받을 수 있는 상황이다. 이로 인하여 생체 간이식이 대안으로 활성화되어 세계적으로 단위 인구당 가장 많은 생체 간이식을 시행하고 있으며, 국내 생체 간이식 프로그램은 아시아는 물론 세계적으로도 선도적인 역할을 하고 있다. 생체 기증자는 간 기증 후에도 간기능에 이상을 초래하지 않는 범위에서 기증 여부와 기증 방법을 결정할 수 있다. 그러나, 생체 간이식은 생체 기증자에게는 아무런 의학적 혜택이 없는 반면 중대한 합병증을 포함한 여러가지 합병증이 발생할 수 있다. 이곳에서는 생체 간기증 자의 장기 예후를 살펴보고, 생체간기증자의 안전 및 삶의 질을 향상시킬 수 있는 방안이 무엇인지 살펴보고자 한다.

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DAY 2: Friday, June 17, 2016 (10:10-12:10) EAST TOWER Room A

KLTS Symposium 2

How Far Extended Criteria for Advanced Hepatocellular Carcinoma in Liver Transplantation?

Chairs : Joo-Seop Kim (Hallym Univ.)
Hee Chul Yu (Chonbuk National Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Is Zero Recurrence Possible? : Predictor of Recurrence after Liver Transplantation for Hepatocellular Carcinoma

Hae Won Lee

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Although the Milan criteria could lower the incidence of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) to about 10%, such morphological parameters still have limitations to predict post-LT tumor recurrence and have excluded a large number of patients who could benefit from LT with an acceptable risk of HCC recurrence. Many recent data emphasized the significance of biological parameters as predictors of HCC recurrence after LT. The combination of morphological and biological parameters might allow approaching to the zero recurrence after LT. In addition, it could reasonably increase the number of transplantable patients and to improve the results in both Milan criteria-in and Milan criteria-out patients.[1]

Histopathological features such as microvascular invasion and tumor differentiation are well-recognized predictive factors.[2,3] Thus, some trials have considered the inclusion of histological findings based on pre-transplant needle biopsy in the patient selection criteria.[3] However, preoperative needle biopsy may increase tumor seeding and post-transplant recurrence.[4] In addition, the presence of these pathological features may not be detected reliably before transplantation in spite of the invasive biopsy procedures.[5]

Several serum tumor markers are considered as prognostic factors after LT for HCC.[6] Alpha-fetoprotein (AFP) is the most well-known tumor marker for HCC and the value of pre-transplant serum AFP level in predicting HCC recurrence has been highlighted by many studies.[1,6] The consensus conference also indicated that serum AFP levels alongside imaging findings may also provide prognostic information in HCC patients and could be used for decision making.[5] Des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist II (PIVKA-II), has been recently utilized as an important tumor marker for HCC, particularly in Japan.[7] Preoperative serum DCP levels were reported as a possible indicator of microvascular invasion in HCC.[8,9] The correlation between high serum DCP levels and post-transplant HCC recurrence has been suggested by multiple recent studies.[10-12] The combination of these tumor markers may predict HCC recurrence better than the conventional criteria based on the size and number of tumors.[6]

Systemic inflammation has been recently linked to poor outcome and higher HCC recurrence after LT.[1] The neutrophil-to-lymphocyte ratio (NLR) has been the most frequently investigated finding. Some studies reported that the elevated NLR significantly correlated with high HCC recurrence rates after LT.[13,14] However, other studies have found conflicting results.[15,16] Although variable inflammatory markers, including C-reactive protein and platelet-to-lymphocyte ratio have been introduced as predictive factors, there is no consensus regarding their use.[6]

Seoul National University Hospital first reported the usefulness of preoperative Fluorine-18-fluodeoxyglucose (FDG) positron emission tomography (PET) to predict post-transplant HCC recurrence in 2006.[17] Subsequently, additional institutions have found a correlation between the hot uptake of 18F-FDG PET and poor outcomes after LT. However, PET has not yet been integrated into the candidate selection process for LT for HCC.[6]

Although no consensus exists regarding the use of prognostic biomarkers and the best cut-off values to adapt, preliminary data suggest that biomarkers such as serum AFP, DCP, and PET positivity may improve the post-LT outcomes and

enable the expansion of the selection criteria for LT for HCC in the near future.[1,6] More studies are needed in order to reach an international consensus.

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Acceptable Guidelines of Liver Transplantation for Advanced Hepatocellular Carcinoma

Chong Woo Chu

Pusan National Univ., Korea

Introduction: The Milan criteria are widely accepted for indicating liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). However, there remains a 7–20% possibility of HCC recurrence, even among patients who fulfill the Milan criteria. It has been shown that tumor biology including differentiation, serum alpha fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKAII) predict posttransplant recurrence and survival better than morphology criteria. And also, downstaging by locoregional therapies of HCC before LT serves as a selection tool. Furthermore, successful downstaging can affect recurrence of HCC by modulation of these biology. We analysis the result of downstaging and correlation with tumor recurrence.
Methods: We retrospectively reviewed 119 patients with HCC who underwent LT at Pusan National University Yangsan Hospital between May 2010 and December 2015. The risk factors for HCC recurrence were analyzed and the overall survival and disease-free survival rates were calculated based on each risk factor.
Results: we defined the A-P 200 criteria as simultaneously exhibiting alphafetoprotein levels of ≤ 200 ng/mL and PIVKA-II levels of ≤ 200 mAU/mL. Multivariate analyses revealed that the independent risk factors for HCC recurrence were Above A-P 200 criteria (HR = 3.776, p = 0.013) and microvascular invasion (HR = 3.781 p = 0.012). The 3-year disease-free survival rates among patients who fulfilled or exceeded the A-P 200 criteria in within Milan criteria were 92.8% and 60.0%, respectively (P = 0.009). And the 3-year disease-free survival rates among patients who fulfilled or exceeded the A-P 200 criteria in above Milan criteria were 89.5% and 35.8%, respectively (P = 0.011). And we intentionally controlled the patient with advanced HCC by neoadjuvant therapy and 23 cases were included into the control group. The control group comparing with 33cases of the uncontrolled group showed significantly lower recurrence rate. (the 3-year disease-free survival rates 95.5% versus 56.1%, p = 0.007). We also retrospective analyzed preoperative radiologic findings and can predict histologic grade and microvascular invasion and reveal the correlation between biologic change and neoadjuvant therapy such as TACE.
Conclusion: The A-P 200 criteria can be used to predict recurrence after liver transplantation among patients with HCC. And successful downstaging can affect recurrence of advanced HCC by modulation of tumor biology (AFP, PIVKAII).

Liver Transplantation for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

Jong Man Kim

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Hepatocellular carcinoma (HCC) is currently ranked as the fifth most common cancer and the third leading cause of cancer death worldwide. If curative therapies, such as hepatic resection, liver transplantation, and radiofrequency ablation, are possible, survival rates can be improved. Despite widespread application of active surveillance programs to detect early stage HCC, a significant proportion of patients are still diagnosed with unresectable HCC or advanced HCC. The lifetime cumulative incidence of portal vein tumor thrombosis (PVTT) was reported to be approximately 1% in a population-based study.

The clinical significance of PVTT in HCC patients has been well documented in a number of previous publications. Briefly, the multicentric nature of HCC is commonly associated with PVTT, and, conversely, PVTT or great vessel invasion in HCC also promotes intrahepatic tumor spreading, leading to disease progression, early treatment failure, or deterioration of liver function. In addition, the existence of PVTT or intrahepatic vascular invasion in HCC is reflected in the national cancer staging system and implies a more advanced and intractable tumor condition.

Although conventional cytotoxic chemotherapy has been used for advanced HCC with vascular invasion or distant metastasis, its efficacy has proven to be poor due to liver toxicity and inherent resistance to cytotoxic drugs. In Korea, intra-arterial chemotherapy, radiotherapy, or concurrent chemoradiation therapy have been tried to control intrahepatic HCC for selected patients with locally advanced HCC. Recently, beneficial responses and excellent outcomes after external beam radiation therapy (EBRT) in HCC patients have been reported, and EBRT is now officially recommended as one of the therapeutic options for inoperable liver cancer by the National Comprehensive Cancer Network guidelines. However, these treatment modalities share the pitfall of a lack of well-designed prospective, randomized, controlled trials. We experienced the small cases who underwent LDLT in HCC with PVTT. Our experience revealed that LDLT following RT can be treatment of choice for PVTT in selective patients.

Adjuvant Therapy for Prevention of Recurrence of Hepatocellular Carcinoma after Liver Transplantation

Jae Min Chun

Kyungpook National University Hospital, Korea

Since Mazzaferro introduced the Milan criteria, these were adopted worldwide as a guideline to liver transplantation (LT) for hepatocellular carcinoma (HCC). However, several groups have argued that the Milan criteria are too restrictive and some new criteria was created expanding Milan criteria. Also, Living donor liver transplantation (LDLT) has become the most effective alternative to deceased donor liver transplantation in Asian countries. As a result, the proportion of HCC patients in adult LDLT in Korea has been dramatically increasing over recent years, reached to 50.3% of LDLT.

Once HCC recurs after LT, the clinical course is dismal with median survival of 9 months. Around 10% of within Milan criteria HCC patient will exhibit post-transplant recurrence and in patients who are beyond Milan criteria, the recurrence rates were reported up to 57%. Recurrence is either due to the growth of preoperatively undetected occult metastases or to the engraftment of circulating tumor cells released at the time of transplantation.

Various therapies have been studied to improve outcomes in the adjuvant setting for HCC recurrence after LT. Among them, sorafenib and Mammalian target of rapamycin (mTOR) inhibitors were at the center of attention and most recently, important results were disclosed.

Sorafenib, which was demonstrated to be associated with survival benefit in patients with advanced HCC, has gained a great attention as a possible agent for adjuvant therapy and a few studies also reported preventive effects of sorafenib. However, STORM study revealed that sorafenib is not an effective intervention in the adjuvant setting for HCC following resection or ablation. These are concerning results for the prospects of sorafenib's efficacy in the adjuvant setting.

mTOR inhibitors also received clinical interest because of their unique activities of immuosuppressive, antiangiogenic, antiproliferative effects, but data relating to an effect of mTOR inhibition are largely restricted to retrospective and non-randomized prospective analyses. In 2016, a large international phase III trial (SILVER) was completed and concluded that though a RFS and OS benefit is evident in the first 3 to 5 years, especially in low-risk patients, sirolimus in LT recipients with HCC does not improve long-term RFS beyond 5 years.

In addition to above two agents, other adjuvant trials using cytotoxic chemotherapy agent, anti-HCC radioimmunologic agent were performed, but these are not conclusive and there is no strong evidence to support the efficacy of treatment mostly due to the scarcity of large RCT.

In conclusion, to reduce the recurrence of HCC after LT, meticulous preoperative evaluation and effort to minimize the intraoperative release of HCC cells are mandatory and we need to discover novel agents that have preventive effects as an adjuvant therapy.

Multi- and Inter-disciplinary Approach for Recurrent Hepatocellular Carcinoma

Dong Jin Joo

Department of Surgery, Yonsei University College of Medicine, Korea

Hepatocellular Carcinoma (HCC) is a difficult liver disease to treat because HCC has characters such as multicentricity, easy recurrence, and various degree of fibrotic background of the liver. Thus, decision about the treatment modality for the HCC patients is hard to make for surgeons or hepatologists. As we know, Barcelona Cancer Liver Center (BCLC) guideline suggests simplifying the treatment algorithm according to the both of tumor status and extent of liver cirrhosis. However, each patient's condition is very widely different and sometimes other treatment option would be better than following the guideline. This is the reason why we have to multidisciplinary approach to decide the HCC treatment.

In terms of liver transplantation, proper timing of the transplantation cannot be easily decided. 'Too early' or 'too late' issues can be occurred. Some hepatologists tend to let time drag on with multiple loco-regional therapy because of worrying the immunosuppressive status after transplantation. On the other hand, some surgeons tend to hurry to perform transplantation because of the recurrence issue of HCC. We do not have any definite answer for that issue. But, this can be a definite reason that various department members who are related to the HCC treatment have to meet regularly and discuss the problem of the same patient.

According to the BCLC guidelines, HCC on the intermediate stage (B) and the advanced stage (C) never have a chance to be performed by curative treatment. Recently, however, down-staging with multi-modal treatment including radiation therapy can give them a good chance to undergo even liver transplantation.

Any single therapeutic approach is not enough to treat the HCC because of its recurrent tendency. Medical team always should watch out recurrence of HCC after first treatment no matter what it was. Thus, liver transplantation should be considered at the time of first diagnosis of HCC, even though it does not have to be considered as a primary treatment. Shortage of brain death donor is a huge hurdle of transplantation in Korea, but it is relatively easier to meet living donor in Korea than in western countries. Living donor liver transplantation can be a good option for the BCLC stage B and C because we can control the time of transplantation and wait the responsiveness after down-staging, which can be a filtering option to exclude worse tumor biology.

My presentation will show literature reviews of the above issues and examples of multidisciplinary approach to the advanced HCC in our center.

DAY 2: Friday, June 17, 2016 (08:30-09:50) EAST TOWER Room BC

KASL-KLCA Joint Symposium

Cure of Hepatitis B Virus and Hepatocellular Carcinoma

Chairs : Mong Cho (Pusan National Univ.)
Joong-Won Park (National Cancer Center)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Hepatocellular Carcinoma: Immune Check Point Blockade

Andrew X. Zhu

Harvard University, USA

Immune checkpoint blockade has recently emerged as a promising therapeutic approach for various malignancies including hepatocellular carcinoma (HCC). Preclinical and clinical studies have shown the potential benefit of modulating the immunogenicity of HCC. In addition, recent advances in tumor immunology have broadened our understanding of the complex mechanism of immune evasion. The author will summarize the current knowledge on HCC immunology and discuss the potential of immune checkpoint blockade as a novel HCC therapy from the basic and translational perspectives, and update the clinical experience with checkpoint inhibitors in HCC.

Immune Engineering toward a Cure of Hepatitis B Virus

Su-Hyung Park

Graduate School of Medical Science and Engineering, KAIST, Korea

For the treatment of chronic HBV infection, nucleos(t)ide analogue antivirals have been successfully used to suppress viral replication. However, HBV exists as a cccDNA, which cannot be eliminated by nucleos(t)ide analogues. Therefore, a practical goal of HBV therapeutics has been HBs seroconversion (loss of HBsAg and development of HBsAg-specific antibodies) and, currently, peg-IFN-a is used to induce HBs seroconversion in patients with chronic HBV infection; however, the efficacy is not satisfactory.

In future, adding to nucleos(t)ide analogues, immunological therapeutic strategies must be developed to cure chronic HBV infection and eliminate cccDNA by eliciting an efficient HBV-specific T or B cell immunity and/or producing antiviral cytokines able to suppress HBV replication. These therapeutic strategies include (i) immunotherapies that can restore HBV-specific T or B cell immunity such as anti-HBs antibodies, immune checkpoint inhibitors, therapeutic vaccinations and adoptive T cell therapies, and (ii) therapies that increase the production or delivery of antiviral cytokines within the liver such as TLR agonists and TCR-like antibodies. In this talk, the rationales and working mechanisms related to new immunological therapeutic strategies for curing chronic HBV infection will be discussed.

New Therapeutic Perspectives for Hepatitis B Virus Cure

Jia-Horng Kao

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Current antiviral therapies have been proven to reduce the progression of chronic hepatitis B (CHB). However, covalently closed circular DNA (cccDNA) of hepatitis B virus (HBV) persists, resulting in viral relapse after the discontinuation of treatment. Several novel agents through viral and host targets approaches are under investigations towards functional cure of HBV. On one hand, direct acting antivirals (DAA) targeting virus itself, such as HBV entry inhibitor, engineered site-specific nucleases and RNA interference, could inhibit intrahepatic HBV infection and eliminate or silence cccDNA transcription. On the other hand, host targeting agents could induce non-cytolytic destruction of cccDNA or attack HBV-infected hepatocytes. With these promising approaches, we hope to reach global HBV control in the middle of this century.

Predictive Molecular Pathology in Hepatocellular Carcinoma: In the Era of Targeted Therapy

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All cancers arise as a result of accumulated genetic and epigenetic alterations. Therefore, analyses of cancer genome sequences and structures provide insights for understanding cancer biology, diagnosis and therapy. The application of microarray or second-generation sequencing technologies is allowing substantial advances in cancer genomics. Thus, our understanding of the complexity of cancer has significantly increased through large-scale genomic studies from large collaborations such as the International Cancer Genome Consortium (ICGC http://www.icgc.org/) and The Cancer Genome Atlas (TCGA http://cancergenome.nih.gov/). However, the translation of these data sets into clinically actionable information is still in its infancy; nevertheless, insights from sequencing studies have led to the discovery of a variety of novel diagnostic and prognostic biomarkers and potentially actionable therapeutic targets. Here, I will present recent development of cancer genomics in liver cancer and discuss what the new findings have taught us about cancer biology and, more importantly, how these new findings guide more effective diagnostic and treatment strategies in liver cancer.

DAY 2: Friday, June 17, 2016 (10:10-11:20) EAST TOWER Room BC

Multidisciplinary Approach to Patients with Transarterial Chemoembolization Failure

Chairs : Yun Hwan Kim (Korea Univ.)
Seung Woon Paik (Sungkyunkwan Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Transarterial Chemoembolization Refractoriness / Failure

Joong-Won Park

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According to current guidelines of most countries, the consensus for standard care for unresectable intermediate stage hepatocellular carcinoma (HCC) is transarterial chemoembolization (TACE). However, the Barcelona Clinic Liver Cancer (BCLC) staging criteria for intermediate stage includes a wide range of liver function and tumor characteristics, and additionally TACE is applied not only to intermediate stage cases but also to advanced or even early stage cases of HCC in practice. A recent global observation study reported that across all stages, TACE was most frequently used first in North America, Europe, China and South Korea. Although TACE as an initial treatment has proven survival benefit in patients with intermediate stage HCC, most of patients treated with TACE as an initial treatment usually have tumor recurrence, residual tumor or even progressive disease. TACE is considered a palliative treatment modality because complete tumor necrosis is rarely achieved, even with repeated treatments. Therefore, subsequent treatment options and TACE refractoriness or failure are unmet clinical issues. Additionally, TACE may cause prolonged depression of liver function in cases of non-superselective TACE techniques, infiltrative types of tumor or Child-Pugh class B patients. There are several definitions of TACE refractoriness/failure from Japan, France, Korea, and Australia; however, there is no consensus among experts regarding the number of previous TACE procedures (2-4 consecutive procedures) and the period over which these procedures are performed that is considered sufficient to define refractory or failed status (3-6 months). It is currently difficult to differentiate TACE-refractory patients from treatment failures, which complicates appropriate patient management. A Korean cohort study suggested that disease progression during the first 6 months after the initial TACE or a requirement for 3 sessions of repeated TACE within the first 6 months might be considered criteria for TACE refractoriness.

Technical issues of TACE treatment include complications of vascular access with difficulty advancing a catheter to the tumor site and atypical hypovascular HCC cases. For patients with these problems, other locoregional treatment including RFA or radiation therapy may be considered. In patients with TACE-refractory stage progression (with the appearance of vascular thrombosis, extrahepatic metastases, and intrahepatic lesions), sorafenib treatment or alternative local treatments should be considered. In cases of toxicity or liver failure, suggesting intolerance to repeated TACE, alternate therapies should be considered.

Rescue Therapies for Transarterial Chemoembolization Failure and Clinical Outcomes in HCC

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Liver cancer is the second cause of mortality from any type of cancer worldwide. Among 5 treatments accepted by guidelines as being effective (surgical resection, liver transplantation, radiofrequency ablation, transcatheter arterial chemoembolization (TACE) and sorafenib), TACE represents the standard of care for patients defined as being at intermediate HCC stage according to BCLC staging system. The natural history of these patients -those with multinodular-liver only tumors, ECOG 0 and Child Pugh A-B class- was defined in several series of 1980-90. Median survival is expected of 16 month, without treatment. Conventional TACE (cTACE) should be applied supraselectively with an emulsion for gelfoam doxorubicin followed by embolization agents. Alternatively DEBead leaded with chemotherapy has shown similar objective response, but there is a lack of long-term comparisons between these two strategies. TACE is effective based upon 2 Randomized controlled studies comparing this treatment versus suboptimal therapies or best supportive care. Afterwards a meta-analysis of 6 RCT confirmed survival advantages for patients treated specifically with chemoembolization, as opposed to bland embolization that has not showed survival advantages. As a result of these studies, TACE is the standard of care for intermediate HCC, and generally is applied a median of 3-4 times per patient. Survival advantages in this setting of trials showed benefits of 4 months (from 16 to 20 months), but more recent trials have reported median survival of around 26-30 months. Ideal candidates are patients with ECOG 0, multinodular unresectable tumors (generally sized below 10cm), no macrovascular invasion or extrahepatic spread. In terms of liver function, ideally patients should belong to Child–Pugh A class or B7 without ascites. Hepato-fugal blood flow is considered a formal contraindication.

During the past 10 years a controversy has emerged on how to manage patients with TACE, when to stop the treatment, and when to switch to other effective therapies. In general, achievement of objective response after 2 TACE is considered the best indicator of improvement in survival. Although this has been the ideal scenario for TACE, some centers and even guidelines have promoted treatment beyond progression as long as reamins intrahepatic. In fact, TACE is the most applied treatment in Asia, for both intermediate and advanced stages, despite the fact that it has not shown benefits in patients with macrovascular invasion of treatment-related symptoms. Therefore, other therapies should be considered once TACE have exhausted the capacity of expanding live expectancy, which should be considered after 2-3 treatments if a measurable response is not in place. In these cases, the natural treatment for TACE failures is sorafenib. Sorafenib was shown effective in the subgroup analysis of SHARP for in intermediate HCC, where this kinase inhibitor expanded survival from 11 to 14 months. This is consistent with the concept of treatment stage migration described in EASL guidelines, where a given treatment should be considered for earlier stages of the disease in case that effective treatment for those sages already failed.

Other therapies compete with sorafenib. This is the case of radioembolization with Y90. This therapy requires high-level equipment in tertiary centers. So far, phase II data in centers of excellence have reported acceptable survival rates for Y90, but trials comparing head-to-head with TACE failed recruitment. Conversely, there are currently several trials challenging sorafenib with Y90, and the final phase III results are expected in the following months. The best survival results with Y90 have been reported in patients with portal vein invasion, where mean survival of around 9 months was achieved in cohort studies. Phase III trials confirming these results are awaited. Other alternatives to sorafenib are molecular targeted therapies and immunotherapies. Regorafenib has been reported to be effective in patients progressing to sorafenib, in the setting of a phase III RESORCE trial in second line. Full information of this study will be available in short. Finally, immunotherapy, particularly with checkpoint inhibitors – such as nivolumab- have been reported to achieve objective response of 16% and median survival of 14 month in single arm large studies.

Radiation Therapy as a Potential Modality for Patients with Transcatheter Arterial Chemoembolization Failure

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Transcatheter arterial chemoembolization (TACE) has been widely used as non-curative therapy for hepatocellular carcinoma (HCC) cases that are non-surgical or unsuitable for local ablative therapies. However, TACE alone rarely produced a complete response and additional treatments are often required. Modalities such as RFA, PEI, sorafenib, conventional radiotherapy (RT) and stereotactic ablative radiotherapy (SABR) have been suggested in addition to TACE, but a definitive guideline has not been established.

The role of RT in HCC is limited owing to the liver's low tolerance to radiation and the risk of radio-induced liver damage. However, recent radiotherapeutic developments have gradually expanded the indications for external beam radiotherapy from palliative to curative aim. With the introduction of SABR, recent clinical data have demonstrated the feasibility of SABR for HCC treatment with high local control and overall survival rates and low treatment-related severe toxicities.

Through this lecture, I will show that combining SABR to incomplete TACE offered the survival benefits over repeated TACE, suggesting that SABR might be recommended as a treatment modality after TACE failure. However, since all previous studies included retrospective or Phase I/II studies, multicenter randomized controlled trials are mandatory to approve the potential benefits of SABR as an alternative modality in the treatment of HCC after incomplete TACE.

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DAY 2: Friday, June 17, 2016 (13:10-15:15) EAST TOWER Room BC

KLCA-KHBPS Joint Symposium

Optimal Management of Recurrent Hepatocellular Carcinoma after Resection

Chairs : Kwan Sik Lee (Yonsei Univ.)
Kyung-Suk Suh (Seoul National Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Follow-up Protocol after Resection: Risk-based or Unified

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The risk of post-resection hepatocellular carcinoma (HCC) recurrence is widely variable according to the preoperative tumor burden and remnant liver status. It is simply present as "The higher the estimated risk is, the more frequent follow-up should be." However, so far, any reliable post-resection follow-up protocol has been not provided yet. Some valuable information on tumor biology of HCC is obtained from comparison between liver resection (LR) and liver transplantation (LT) for HCC. First, if viable tumor volume is very low (e.g., single small HCC or complete pathological response), the risk of extrahepatic recurrence is very low. In contrast, intrahepatic recurrence following LR occurs in a considerable rate as either recurrence or de novo development. Following LT, small tumors with low expression of tumor markers showed low recurrence rates, but late recurrence occurred sporadically. They usually respond well to recurrence treatment. Therefore, patients with low tumor burden may be indicated for life-long surveillance with prolonged follow-up intervals. Second, patients with high tumor burden (e.g., large tumor, multiplicity, macroscopic vascular invasion or high expression of tumor markers) have high risk of early tumor recurrence at the remnant liver or other organs. These patients should be followed up frequently especially during the first year; as time goes, a majority may pass away due to tumor progression. Transcatheter arterial chemo-infusion/embolization at 1 month after LR is reasonably indicated for patients with high risk. Third, disease-free period after LR may reflect the tumor biology, thus prolonged disease-free period may lead to prolongation of follow-up intervals. Fourth, tumors showing high expression of tumor markers may also produce tumor markers abundantly, thus tumor marker monitoring can lead to early diagnosis of recurrence in a higher probability. Considering these background information, the post-resection follow-up protocol can be summarized as follows: During the first 6 months, the interval of follow-up be set 1 to 3 months depending on risk; until 1 year, it can be adjusted to 2-3 months; from 1 year to 3 years, it may to settled to 3 months; thereafter, it may be prolonged to 3-4 months unless recurrence happens; As a life-long long-term follow-up, if preoperative tumor makers are high, frequent follow-up of tumors markers with less frequent imaging study may be reasonable from the viewpoint of cost-effectiveness and patient compliance. Otherwise, risk-adjusted regular imaging studies should be performed to detect the recurrent lesions in time. Since LR is regarded as a local control of the primary tumor, other conditions vulnerable to tumor recurrence or de novo development are still remained. Therefore, it is reasonable to design individually customized post-resection follow-up protocol based on risk of recurrence, which can be later adjusted according to the functional status of the liver, duration of disease-free period and patient compliance.

Locoregional Therapy for Recurrent Hepatocellular Carcinoma after Resection

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간절제술 후 재발한 간세포암종의 국소 치료

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서론

간세포암종은 전 세계적으로 유병률 다섯 번째인 악성 종양이며 악성종양과 관련한 사망률에서는 세 번째를 차지하는 주요 암종이다.[1]

간세포암종이 진단되었을 때 치료 방향은 종양인자, 잔존 간기능, 환자의 수행능력과 동반 질환을 모두 고려하여 결정 되어진다. 특히 간세포암종은 여느 암종과 달리 B형 간염, C형 간염, 알코올성 간질환, 특히 간경변증을 동반 하는 것이 대부분이어서 일률적인 치료 방침을 결정 하는 것이 매우 난해 하며 그로 인해 전세계의 여러 가이드라인이 서로 상이한 치료 알고리즘을 제시 하고 있는 것이 사실이다.[2-4] 그렇다 하더라도 모든 간세포암종을 진단 받은 환자는 가능한 근치적 치료법을 받을 수 있는 방향으로 치료 방침이 고려 되며 그에 부적합한 이유가 있는 경우는 고식적 치료법을 선택 하게 된다.

간세포암종의 근치적 치료법에는 간이식, 간절제술, 국소치료술이 있다. 간이식의 경우에는 재발률이 10% 이하이지만 간절제술과 국소 치료술은 근치적 치료로 고려 됨에도 불구하고 재발률이 5년에 70%까지 보고되어 왔다.[5]

따라서 근치적 치료인 간절제술을 받고 재발한 환자에서 이후 어떤 치료를 하는 것이 바람직하며 가장 환자의 예후에 좋은지가 중요한 문제이다. 간절제술후 재발 환자에 고려 되고 있는 치료법은 구제적 간이식, 재 간절제술, 국소치료술등이 다시 일차적으로 고려 되고 있으며 그에 적합하지 않은 환자에겐 고식적 치료가 시행 되고 있다. 하지만 이들에서 어떤 치료가 더 적합한지, 재발 환자에서도 초치료와 유사한 전략이 적용 되는 것이 적절 한지에 대한 연구는 매우 부족한 것이 현실이다.

이 논고에서는 간절제술 후 재발한 환자에서 간세포암종의 치료에 대한 연구를 간략히 요약해 본후 국소치료에 속하는 국소치료술과 경동맥항암색전술의 근거에 대해 논의해 보고자 한다.

본론

간절제술후 재발한 간세포암종의 치료가 어떻게 이루어져 왔는지에 대해 구체적으로 분석한 보고는 거의 없다. 하지만 간절제술후 재발한 간세포암종에서 이후 수술등의 특정 치료를 한 경우에 대한 분석 연구에서 개괄적인 다른 치료를 언급하고 있어 간접적인 경향은 확인 해 볼 수 있다. Zhou 등[6]의 연구에서 429명의 간절제술후 추적 되었던 환자 중 276명(64.3%)에서 재발이 확인 되었고 그 중 재 간절제술을 받은 환자는

37명(13.4%) 였으며 경동맥화학색전술을 받은 환자는 126명(45.6%), 국소치료술을 받은 환자는 45명(16.3%)이었으며 보존적 치료만 받은 환자는 68명(24.6%)였다. Wu 등[7]의 연구에서는 1177명의 간절제술 후 추적 되었던 환자 중 641명 (54.5%)에서 재발이 확인되었고 그 중 재 간절제술을 받은 환자는 149명(23.2%) 였으며 경동맥화학색전술을 받은 환자는 388명(60.5%), 국소치료술을 받은 환자는 63명(9.8%)이었으며 전신항암치료를 받은 환자가 10명(1.6%) 보존적 치료만 받은 환자는 6명(0.9%) 였다. Ho 등[8]의 연구에서는 980명의 간절제술 후 이식 없이 추적 되었던 환자 중 476명 (48.6%)에서 간내 재발이 확인 되었고 그 중 재 간절제술을 받은 환자는 54명(11.3%) 였으며 경동맥화학색전술을 받은 환자는 254명(53.3%), 국소치료술을 받은 환자는 50명(10.5%)이었으며 보존적 치료만 받은 환자는 77명(16.2%)이었다.

이들 연구에서 확인할 수 있는 것은 재발 이후에 치료 방법의 결정도 초 치료시의 결정과 크게 다르지 않아 재간절제술, 국소치료술, 경동맥화학색전술등의 선택이 초치료의 선택과 유사한 분율로 이루어지고 있다는 것을 알 수 있다. 하지만 이들을 서로 비교한 연구가 없어 초치료와 같은 전략으로 접근 하는 것이 재발한 간세포암종 환자에서도 적절한지에 대한 논의는 제한된 상황이다. 하지만, Chan 등[9]은 구제적 간이식과 재 간절제술, 재 국소소작술을 비교 한 결과를 보고 하였다. 532명의 간절제술 또는 국소치료술 후 추적 되었던 환자 중 288명(54.5%)에서 재발이 확인 되었고 그 중 간내 재발환자는 183명이었다. 간내 재발 환자 중 구제 간이식을 받은 환자는 19명(10.4%), 재간절제술을 받은 환자는 24명(13.1%) 였으며 경동맥화학색전술을 받은 환자는 47명(25.7%), 국소치료술을 받은 환자는 57명(31.1%) 이었으며 전신항암치료를 받은 환자가 7명(3.8%) 보존적 치료만 받은 환자는 29명(15.8%)이었다. 이 연구에서 구제적 간이식과 재 간절제술, 재 국소소작술을 받은 혼자의 5년 무재발 생존율은 각각 40%, 19.8%, 10.6%로 재 국소소작술을 받은 환자에 비해 구제적 간이식과 재 간절제술을 받은 환자에서 예후가 유의하게 좋았다. 하지만 이들에서 MELD 스코어도 의미 있는 차이를 보였기 때문에 이를 보정 하여 확인 하였으나 역시 5년 무재발 생존율은 각각 50%, 48%, 11%로 재국소소작술을 받은 환자에 비해 구제적 간이식과 재 간절제술을 받은 환자에서 예후가 유의하게 좋았다. 다만, 제한된 조건의 후향적 연구로 어느 치료의 우수성을 논하는 것은 적절 하지 않아 이에 대한 더 많은 연구가 필요하다.

간절제술후 재발한 간세포암종의 국소치료술을 시행한 연구는 고주파열치료술이 주를 이루며 에탄올주입술과 냉동소작술, 고강도집속초음파치료(HIFU) 등이 보고되어 있다.[8,10-28] 이들 연구에서 B형 간염이 동반된 경우가 85%(8-96%)로 대부분 동양에서 이루어진 연구였으며 환자의 80%(23-100%)가 Child-Pugh A등급이었고 B가 12%(0-69%)로 간절제술을 받은 환자인 만큼 간기능은 대체로 잘 보존 되어 있었다. 재 국소치료술 이후 전체 생존 기간과 무병 생존 기간은 각각 48개월(31-66개월)과 10개월(4-17개월) 로 보고 되고 5년 생존율은 40% (28-83%)였다. 재 국소치료술 후 완전 치료 반응률은 69-97%까지 보고되었다. 재국소치료술후 다시 재발한 경우 재 치료 부위 재발이 11%(3-17%), 원위 간내 재발이 66%(37-95%) 그리고 간외 재발이 17%(5-42%) 였다. 재 국소 치료술 후 유의한 부작용의 발생은 전체 보고에서 2.9% (35/1188) 정도였으며 출혈, 간농양과 치료 부위 및, 심장, 폐의 부작용이 보고 되었다. 예후 관련 인자 분석에서 다양한 인자가 보고가 되었으며 그 중 알파태아단백을 100 또는 200 ng/mL를 기준으로 하는 것이 대체로 공통적인 생존 관련 인자로 나타났다. 이들 연구는 대부분 후향적 코호트 연구로 재 국소치료술의 의의를 충분히 설명 해 줄 수 없으나 대체로 초치료에서 시행 되는 경우와 유사한 정도의 효과와 부작용을 기대 할 수 있다는 정보를 주고 있다. 한 연구에서 재 국소치료술과 함께 경동맥 화학색전술을 시행 하는 것의 의의에 대해 재 국소치료술과 비교한 전향적 조절 연구가 있었다.[13] 139명의 간절제술 또는 국소치료술 후 치료 부위 이외에서 재발한 5cm 이하의 환자를 무작위 배정하여 69명은 국소 치료술과 함께 경동맥화학색전술을 시행하고 70명은 국소치료술을 시행하였다. 1년, 3년, 5년 전체 생존율이 재국소치료술과 함께 경동맥화학색전술을 시행한 경우 94%, 69%, 46%였고 국소치료술만 시행한 경우 82%, 47%, 36%로 의미 있는 차이가 있었다($p = 0.037$). 1년, 3년, 5년 무재발 생존율도 재국소치료술과 함께 경동맥화학색전술을 시행한 경우 80%, 45%, 40%였고 국소치료술만 시행한 경우 64%, 18%, 18% 로

의미 있는 차이가 있었다(p = 0.005). 이는 근치적 치료 후 재발시 국소치료술과 함께 경동맥화학색전술을 함께 시행 하는 것이 국소치료술 단독 보다는 유리 할 수 있다는 것을 보여 준다.

초치료에서와 마찬가지로 재발 종양의 치료에서도 국소치료술은 간절제술과 비교 될 필요가 있다. 이에 대해서는 전향적 조절 연구가 없으며 Chan 등[9]은 간절제술이 우수함을, Kawano 등[25]은 국소 치료술이 우수할 수 있음을 보고 하였으나 그 외 많은 연구는 유사하다고 보고 하고 있다.[8,14,17,26,27]

간 절제술후 재발한 환자에서 경동맥화학색전술을 시행 한 경우에 대한 연구는 많지 않다.[28-30] Poon 등[28]은 244명의 간절제술 환자중 105명이 간내 재발을 보였으며 그들 중 재 간절제술을 받은 환자는 11명, 경동맥화학색전술을 받은 환자는 71명이었고 알코올주입술이 6명 전신항암치료가 8명 그리고 보존적 치료를 9명이 받았다고 보고 하였다. 이 다섯 그룹의 예후를 비교 하였는데 1년, 3년, 5년 생존율이 각각 80.8%, 69.3%, 69.3% vs. 72.1%, 38.2%, 20.9% vs. 66.7%, 22.0%, 0% vs. 37.5%, 0%, 0% vs. 0%, 0%, 0%였다고 보고하면서 간절제술 환자가 경동맥화학색전술을 받은 환자보다 예후가 좋은 경향을 보였으며(p=0.085) 전신항암치료나 보존적 치료를 받는 경우 보다 간절제술, 경동맥화학색전술, 알코올주입술을 받는 환자가 예후가 유의하게 좋다고 보고 하였다. Okazaki 등[29]은 간절제술후 재발로 경동맥화학색전술을 받은 68명 환자의 예후를 보고하였다. 전체 생존율은 1년, 3년, 5년에 각각 87.1%, 34.3%, 0% 이며 평균 생존기간은 947일 정도라고 보고하였다. 이 연구에서 재발한 간세포암종의 혈관조영술상 38.2%의 환자에서 적어도 하나 이상의 간동맥 이외의 혈관을 통해 조영되는 종양이 있었다고 보고 하면서 조영술시에 주의를 요한다고 언급 하였다. Takayasu 등[30]은 270명의 간절제술을 받은 환자 중 재발하여 경동맥화학색전술을 받은 50명의 예후를 보고하였는데, 전체 생존율은 1년, 3년, 5년에 각각 64%, 24%, 5% 이며 평균 생존기간은 947일 정도라고 보고 하였다. 예후에 미치는 독립적 인자는 재발의 양상과 원격 전이 유무였다.

결론

간세포암종은 기저 간질환으로 인해 근치적 치료인 간절제술을 시행 받는 환자에서도 높은 재발률이 보고되고 있다. 따라서, 이들 재발을 막기 위한 많은 노력이 이루어져 왔다. 가장 기본적인 재발의 억제 방법은 B형, C형 간염을 치료 하는 것이라는 것은 잘 알려져 있다. 하지만 이미 이들 발암 인자에 오랜 기간 노출 된 간세포암종 환자에서 재발을 막는데에 원인 질환 치료 만으로는 부족 할 것으로 보여 항암제인 소라페닙,[31] 면역 치료,[32] 비타민 A 유사체 등[33,34]이 보조 치료로 연구되었다. 하지만 소라페닙은 예방 효과를 증명하지 못했고 비타민 A유사체는 최근에야 추가 연구가 이루어지고 있어 아직 유용성을 확인 하기 어렵다. 면역 치료에서는 최근 국내에서 발표된 연구에서 그 효용성이 입증 되었다 하나 임상에서 사용 하기에는 여러 제약이 있는 것이 사실이다. 따라서 재발한 환자에 대한 가장 적절한 치료를 통해 예후 향상을 기대 하는 것이 일차적 목표라 하겠다. 안타깝게도 전술한 바와 같이 재발한 환자에서 어떠한 치료가 가장 적합한지에 대한 연구는 매우 부족하고 따라서 일반적으로 받아들여지는 알고리즘도 없는 상황이다. 하지만 현재까지 보고를 토대로 볼 때 초치료 환자에서와 유사한 기준을 통해 치료 방향을 정하여 치료 하는 것은 재발 환자에서도 유용한 방법일 것으로 보이며 향후 이에 대한 많은 연구가 있기를 기대한다.

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Re-resection: Indication and Limitation

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In 2013, the hepatocellular carcinoma (HCC) is the 4th most common cancer in male and 6th in female. However annual incidence of liver cancer in the whole of the patient men and women has been reduced by 2.3% every year. According to our data,[1] the Disease-Free Survival (DFS) rate after liver resection was 70.4% for 1 year, 48.4% for 3 years,42.2% for 5 years, and 35.5% for 10 years. The median DFS was 35 months. Since above 50% of patients relapse within three years, it is very important to determine the treatment policy for the patients with recurrence.

A systematic review and meta-analysis were performed to compare the post-recurrence survival with hepatic re-resection versus transarterial chemoembolization (TACE) for recurrent HCC after initial resection.[2] Hepatic re-resection might provide a better post-recurrence survival than TACE for recurrent HCC after initial resection. However, considering the low quality of published studies and the potential bias of treatment selection, further randomized trials should be warranted to confirm these findings.

Recently a literature search was performed to identify comparative studies addressing outcomes of both RFA and surgical re-resection for recurrent HCC meeting the Milan criteria.[3] Although RFA seemed to be superior to surgical re-resection in above situation, these findings have to carefully interpreted due to lower level of evidence.

The 5 year survival rate of patients who undergo re-resection of intrahepatic recurrence after initial surgery ranges from 37% to 70%. The result of re-resection is also excellent in cases with a long interval between initial surgery and tumor recurrence.

In 2014 Korean Liver Cancer Study Group-National Cancer center Korea Practice Guideline for the management of HCC, re-resection can be recommended particularly for patients with late intrahepatic recurrence 1-2 years after initial resection as long as vascular invasion of the tumor is not evident and liver function is tolerable to re-operation.[4]

However, until now, optimal guideline for postsurgical recurrence of HCC has not been clearly established. Before evaluation of treatment modalities for recurred HCC patients, we reviewed our previous 10-year experience. From January 2005 to December 2014, 197 medical records of the patients who were revealed intrahepatic recurrence after curative resection for HCC were retrospectively reviewed. Recurrence date and treatment modality after the recurrence were analyzed. Overall survival (OS), disease free survival (DFS) and distant metastases free survival (DmFS) were analyzed. Median DFS was 16.0 months (95% CI 12.0-19.0) and median OS was 108.0 months (95% CI 85.5-130.5) (Fig. 1, 2). DFS was 89.5 months (95% CI 82.5-97.2) (Fig. 3).

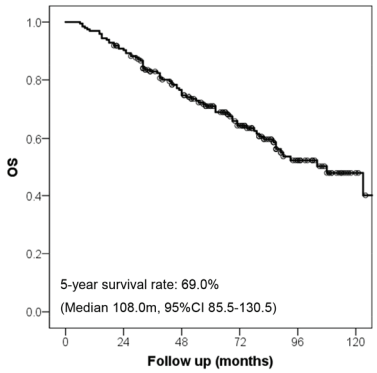

Figure 1. Overall survival rate of recurrent patients after curative resection

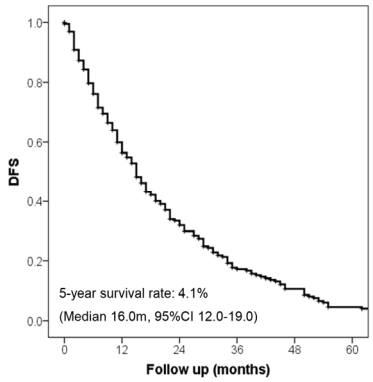

Figure 2. Disease free survival rate of recurrent patients after curative resection

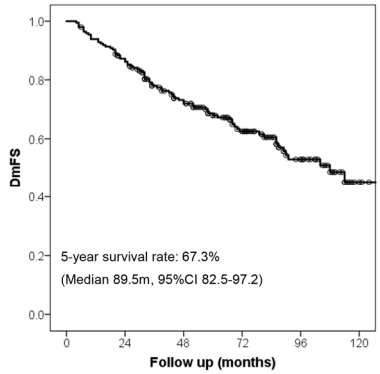

Figure 3. Distant metastases free survival (DmFS) rate of recur

During the period, mean recurrence times was 3.7 ± 1.7 and 94 (4Z7.7%) patients experienced multiple treatment modality(Table 1).

Treatments at the time of the first recurrence were as follow. (Resection: 15 (7.6%), RFA: 30 (15.2%), TACE: 134 (68.0%), TARE: 2 (1.0%), cryoablation: 1 (0.5%), RTx.: 1 (0.5%) and TACE + RFA: 13 (6.6%) (Table 2).

Table 1. Basal characteristics of recurrent patients after curative resection

	n=197
Median follow up duration (m)	63.9 ± 31.7
Gender (M:F)	171 : 26 (6.6 : 1)
Age (1st Op.) (yr)	56.1 ± 10.4
BMI	24.1 ± 3.1
Etiology	
Alcohol	6 (3.0%)
HBV	163 (82.7%)
HCV	16 (8.1%)
HBV + HCV	6 (3.0%)
Non-B, Non-C	6 (3.0%)
C-P Classification	
A	192 (97.5%)
B	5 (2.5%)
C	0 (0.0%)
1st resection	
Major (≥3 segments)	91 (46.2%)
Minor (<3 segments)	106 (53.8%)
OS (m)	108.0 (85.5-130.5)
1st DFS (m)	16.0 (12.0-19.0)
DmFS (m)	89.5 (82.5-97.2)
Mean recurrence times	3.7 ± 1.7
Recurrence treatment portion (n=540)	
Resection	32 (5.9%)
LT	14 (2.6%)
RFA	107 (19.8%)
TACE	359 (66.5%)
TARE	3 (0.6%)
Cryoablation	7 (1.3%)
RTx.	18 (3.3%)
Type of treatment modality	
Single	103 (52.3%)
Multiple	94 (47.7%)

Table 2. Characteristics of 2nd treatments after recurrence

	n=197
Age (2nd Tx.) (yr)	57.9 ± 10.4
1st DFS (m)	16.0 (12.0-19.0)
2nd Tx.	
Resection	15 (7.6%)
LT	0 (0.0%)
RFA	30 (15.2%)
TACE	134 (68.0%)
TARE	2 (1.0%)
Cryoablation	2 (1.0%)
RTx.	1 (0.5%)
TACE+RFA	13 (6.6%)
2nd DFS (m)	42.0 (35.5-48.5)
Interval DFS (m)	15.0 (11.4-18.6)

After first intrahepatic recurrence of HCC, most of patients were underwent various treatment more than 5 years. During the periods, optimal treatments guideline for the patients was needed.

Keywords

Hepatocellular carcinoma, recurrence, intrahepatic, therapy modalities, survival rate

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Salvage Liver Transplantation: Role and Limitation, Optimal Patient Selection

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For patients presenting with early stage hepatocellular carcinoma (HCC) and preserved liver function, the optimal initial treatment is still a matter of debate. Some advocate primary liver transplantation (LT) for these patients since it yields the best recurrence-free survival and patients survival rate. However, organ shortage is undoubtedly a major obstacle so in regions of high HCC prevalence often choose liver resection as primary treatment option and save salvage LT for those patients who recur or develop decompensated cirrhosis following liver resection.

The "resect first" salvage LT strategy offers several advantages in a clinical situation of initially transplantable HCC. Liver resection is a readily available, and involves less operative morbidities compared to LT while LT has a higher perioperative morbidity and mortality, need life-long immunosuppression and cannot be done until a compatible donor is available. For the community, the scares graft may be offered more selectively for patients who recur after resection or for to patients who do not have any other means of treatment besides LT.

Although salvage LT had significantly longer operative time and postoperative blood loss in a recent meta-analysis incorporating the data from 14 studies including 236 salvage LT, there were no differences in postoperative morbidity, biliary complications, arterial thrombosis and perioperative mortality.[1] Moreover, in a recent intention-to-treat analysis in patients with initially transplantable HCC, liver resection followed by salvage LT showed similar 5- and 10-year overall survival of these patients compared to primary LT.[2] Therefore, salvage LT should not be considered as inferior to primary LT.

Milan criteria has been a long standing golden standard as selection criteria for HCC in primary LT and most use the same selection criteria for salvage LT. However, it has been shown that the pathologic characteristics of the HCC, such as the presence of microvascular invasion is quite different in salvage LT from primary LT and its presence profoundly affects the outcome.[3] There is still no "golden" selection criteria for best selection of salvage LT.

Recently biological characteristics such as AFP, PIVKA, PET positivity, and the response to transarterial chemoembolizatation (TACE) has been shown to greatly impact the risk of recurrence after primary LT and many centers have started to incorporate it in the selection process. The same seems to be true for salvage LT. AFP less than 200 ng/mL at time of salvage LT fared better (5-year recurrence free survival of 68% vs. 16% in those above 200 ng/mL) and patients who recur within 8 months after primary resection are doomed for poor prognosis (20% 5-year survival vs. 80% for patients who recur after 8 months) [4] Since this group of patients that have multiple risk factors of HCC recurrence do poor, some advocate a preemptive salvage LT for patients that are most likely to fall into this group (tumor size >3 cm, poorly differentiated, vascular invasion, satellite nodules, and cirrhosis) [2]

Salvage LT should be regarded differently from primary LT since a different group of patients are being involved. Surgeons should take care not to just incorporate the "golden Milan criteria" when selecting patients for salvage, but look at the whole picture of "biological nature" of HCC in order to have the best post-operative outcome.

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Rebuttal with Case Discussion

Jeong Heo

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Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the third leading cause of cancer death worldwide. Recurrence rates after curative intent-treatment for HCC are high; 5-year disease-free survival ranges from only 19 to 81%. There is no direct evidence to guide the optimal surveillance and management for recurrent HCC after curative intent treatment. In theory, if an HCC recurrence is discovered early, more therapeutic options are available for treatment of the recurrent HCC. As such, close surveillance after curative intent-therapy may have the potential to prolong survival. Therefore, although data remain scarce, close surveillance with a-fetoprotein and cross-sectional imaging every 3-4 months for 3 years after curative intent-therapy, followed by surveillance every 6-12 months thereafter, seems the most prudent approach to follow-up of patients with HCC in the postsurgical setting.

Currently, the most realistic approach in prolonging survival after resection of HCC is early detection and aggressive management of recurrence. There is little of convincing evidence for the efficacy of neoadjuvant or adjuvant therapy in preventing recurrence. For the management of postoperative recurrence, the treatment modality for recurrent HCC was generally dependent on the extent of first resection, the underlying liver status, and the pattern of recurrence, location of recurrence. The second resection was generally offered as the treatment of choice to patients with a solitary recurrence or a limited number of recurrences confined to the liver, provided the liver function reserve was satisfactory and the recurrent tumors were anatomically resectable. Otherwise, liver transplatation would be an option in the patient without extrahepatic recurrence. Radiofrequency ablation/percutaneous ethanol injection and transarterial chemoembolization are widely used to prolong survival in patients with unresectable intrahepatic recurrence, and combined therapy with these two modalities may offer additional benefit. For extrahepatic recurrence, surgical resection is an effective option for patients with isolated extrahepatic recurrence, although the number of study is limited.

DAY 2: Friday, June 17, 2016 (15:15-15:30) EAST TOWER Room BC

Korea Central Cancer Registry

Chair : Soon Ho Um (President of KLCA)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Hepatocellular Carcinoma Random Sample Analysis Report

Young-Suk Lim

The Liver Cancer Registry Committee of KLCA, Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Korea

To provide evidence-based interventions in prevention, early diagnosis, treatment and palliative care, a national cancer control program is needed, and a population-based cancer registry is an essential element in national cancer control program in evaluating the current situation, setting objectives, and defining priorities.(Parkin 2008)

Populations are all people in a defined setting. Clinical populations include all patients with specific clinical characteristics such as hepatocellular carcinoma (HCC). A sample is a subset of people in the defined population. Researchers are interested in the characteristics of the defined population, but, for practical reasons, must estimate them by describing the characteristics of people in a sample. Thus, clinical research is ordinarily carried out on sample. We then make an inference, a reasoned judgment based on data, that the characteristics of the sample resemble those of the parent population. The extent to which a sample represents its population, and thus is a fair substitute for it, depends on how the sample was selected. Samples taken erroneously may misrepresent their parent population and so be misleading. Thus, random selection of the sample from the population is key essential first step to ensure that the sample can represent the population.

The Korean Liver Cancer Association (KLCA) has its own primary liver cancer registry (available at www.plcr.or.kr). This registry is based on voluntary reporting from the KLCA members, which is a web-based on-line registration registry since year 1990. KLCA voluntary registry has strength as it collects detailed information about the patients, tumors, and treatments. Nevertheless, as a voluntary reporting system, this registry is prone to serious selection bias.

The largest nationwide cancer registry in Korea is the Korea Central Cancer Registry (KCCR), executed by government-endorsed organization, which began cancer registry since 1980. The KCCR registry is statutory registry, and in Korea, patients diagnosed with cancer receive additional economic assistance by a medical reimbursement policy when registered at the KCCR; hence, almost all the incident cancers (> 95%) occurring in the population are reported in the registry. (Ahn 2007) KCCR registry has strength as it has case completeness defined as including all the incident cancers occurring in the population in the registry database, but has limitation as it lacks data completeness; it does not collect detailed information on clinical and tumor characteristics as well as treatment information.

Thus, in the year 2010, the KLCA HCC registry committee decided to conduct a random sample audit from KCCR registry, in order to collect unbiased information about the characteristics of the patients with HCC in Korea. Now, the KLCA has a large database of patients with HCC as follows:

- KLCA voluntary registry for patients diagnosed as HCC between 1990-2015
- KCCR random sample registry for 15% of patients diagnosed as HCC between 2003-2005 in Korea
- KCCR random sample registry for 13% of patients diagnosed as HCC between 2008-2010 in Korea
- KCCR random sample registry for 13% of patients diagnosed as HCC between 2010-2012 in Korea

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DAY 2: Friday, June 17, 2016 (16:30-17:30) EAST TOWER Room BC

Emerging Therapies for Hepatocellular Carcinoma

Chairs : Jae Seok Hwang (Keimyung Univ.)
Jung-Hwan Yoon (Seoul National Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Searching for Biomarker-driven Therapy for Hepatocellular Carcinoma

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Despite the substantial effort to conquer cancer for several decades, the prognosis of hepatocellular carcinoma (HCC) still remains poor. To improve clinical outcome of HCC, a number of putative biomarkers have been investigated for surveillance, diagnosis, prognosis, and therapeutic decision of HCC. However, biomarkers have not been introduced into clinical practice guideline of HCC because of limitation in diagnostic value. The cutting-edge omics technologies and bioinformatics analysis allow to identify molecules involved in the complex pathways regulating the development and progression of HCC. Several biomarkers have been identified through a various methodology and evaluated in different clinical settings. Expression of a number of proteins has been investigated by immunochemical staining in blood and tumor tissues. Gene signatures with prognostic potential have been identified by gene expression profiling from tumor tissue. Recently, frequent genetic mutations in HCC have been found by next generation sequencing and their therapeutic relevance has been evaluated. However, unfortunately, the most published biomarkers are inadequate to replace a traditional clinical test and remained as a temporary laboratory discovery. Although an inherent limitation of each technique certainly exists, the most important aspect of a successful biomarker discovery is that there are no a perfect biomarker with 100% sensitivity and specificity. A single biomarker alone could not indicate our complex disease characteristics nor accomplish with the performance required for clinical test. Therefore, the future of biomarkers most probably is to use a combination of multiple biomarkers to improve accuracy. This presentation gives an overview on current status and limitation of biomarker research in HCC and introduction of our ongoing studies for biomarker-based therapy.

Molecular Targeted Therapy for Hepatocellular Carcinoma: Learning from Genome-matched Trials in Other Solid Cancers

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Sungkyunkwan University, Samsung Medical Center, Korea

Molecular profiling of actionable mutations in refractory cancer patients has the potential to enable "precision medicine," in which individualized therapies result in improved treatment outcomes. However, its clinical benefit in practice has not been clearly demonstrated in large cohorts with multiple cancer types.

The NEXT (Next generation pErsonalized tX with mulTi-omics and preclinical model) trial is a master protocol to route participants to different candidate drugs in trials based on clinical sequencing report. In this trial, we used a customized targeted enrichment panel consisting of cancer-related genes to interrogate single nucleotide variants (SNVs), insertions and deletions (Indels), copy number variants (CNVs) and a subset of gene fusions, that were of clinical significance. In this master protocol, the response rate was assessed as the primary end point in patients who had molecularly-matched or standard therapy. Immunohistochemical staining was performed on MET, PTEN, EGFR, and HER2. From August 2014 through April 2015, 541 patients consented to participate in precision oncology clinic at a single center. Of 541 patients, 94 patients were excluded and 418 cancer patients had sequencing data available to clinician for guidance to matched trials. The patient cohorts were gastric cancer (N = 127), colorectal cancer (N =122), pancreatic/biliary tract cancer (N=62) and sarcoma and cancer (N = 67). Of 418 patients, 159 (38.0%) patients were not treated beyond standard chemotherapy, 187 (44.7%) patients had at least one genomic variant (N=74, no matched therapy available) and 60 (14.4%) patients were successfully routed to genome-based matched clinical trial. In this presentation, matched trials including NEXT-1 and VIKTORY trial with collateral patient derived tumor cell screening program will be presented.

Advances in Percutaneous Ablation Therapies for Hepatocellular Carcinoma

Won Young Tak

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간세포암에 대한 경피적 절제 치료술의 최신지견

탁 원 영

경북대학교 의과대학 내과학교실

국소 절제 치료술은 간세포암 치료에 있어서 매우 중요한 역할을 하고 있다. 국소 절제 치료술은 주로 소간세포암을 치료하는데 이용되고 있다. 고주파 열치료술이 대표적인 치료법으로, 초기 간세포암 치료에 있어서 우수한 치료 성적과 최소 침습적 시술이라는 장점으로 현재 가장 널리 사용되고 있다. 최근에는 냉동 치료술, 극초단파 치료술과 같은 새로운 국소 절제 치료술이 적용되고 있으며 고주파 열치료술을 보완하는 보조적인 기술들이 간세포암 치료에 응용되고 있어 이에 대하여 살펴보겠다.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation, Cryotherapy, Microwave ablation

Local ablation therapies play an important role in the management of hepatocellular carcinoma (HCC). These therapies include radiofrequency ablation (RFA), cryoablation, and microwave ablation, with RFA also being used to treat early-stage HCC[1]. There is strong evidence that RFA is an excellent treatment modality for early-stage HCC, with favorable treatment outcomes and minimal invasiveness. New ablation therapies for HCC such as, cryoablation and microwave ablation and new techniques for assisting ablation therapies have recently been applied to treat HCC. We discuss recent advances in percutaneous ablation therapies for HCC.

1. Radiofrequency ablation

RFA produces coagulative necrosis by exposure to an alternating high-frequency electric current within the radio-frequency range (460 to 500 kHz), which is delivered via an electrode placed in the center of a lesion. This alternating current induces the movement of ions within the tissue that produces frictional heat and leads to cell death. RFA is now considered to be the most favorable ablation treatment for HCC, and its indication has been expanded to include not only HCC but also liver metastases, as well as bridging therapy for HCC before liver transplantation.

(1) Long-term results

There are many published data on treatment outcomes of RFA[1-4], with relatively long-term results for periods of more than 10 years being reported[5-7]. Shiina et al.[6] reported overall survival rates of 96.6%, 80.5%, 60.2%, 45.1%, and 27.3% after 1, 3, 5, 7, and 10 years, respectively, and corresponding rates of distant recurrence without local tumor progression of 25.6%, 63.3%, 74.8%, 78.1%, and 80.8%. Similarly, Kim et al.[7] reported overall survival rates of 95.5%, 77.9%, 59.7%, 43.2%, and 32.3%, and recurrence-free survival rates of 66.8%, 29.0%, 17.5%, 7.0%, and 3.8% after 1, 3, 5, 8, and 10

years, respectively.

(2) Nontouch technique

Seror et al.[8] recently reported long-term results for 108 HCC patients based on the Milan criteria. After a median of 40.5 months of follow-up (range, 2-84 months) the progression-free survival rate was 96%, while the 3-year local, 5-year local, and overall tumor progression-free survival rates were 94%, 52%, and 32%, respectively. They concluded that multibipolar RFA for HCC tumors that meet the Milan criteria will produce a high local tumor progression-free survival rate.

2. Recent ablation methods

(1) Cryoablation

Cryoablation is an ablation technique utilizing cryoprobes targeted at tissue and liquid nitrogen at -196℃, which results in freezing the lesion to at least -35℃ and the formation of ice crystals within cells and thereby disruption of their membranes. However, this early form of cryoablation had a high rate of complications. An argon-helium super-conducting targeted surgical system (Endocare®, Irvine, CA) that ablates tumors by combining freezing and heating mechanisms was recently developed, and it was found to be possible to predict the margin of the ablated zones.

(2) Microwave ablation

Microwave ablation is the most recent method in the field of tumor ablation. It involves ablating a liver tumor by exposure to microwave electromagnetic energy above 900 kHz as generated by a microwave coagulator and transmitted to a monopolar-type needle electrode that is inserted into the lesion The energy induces molecular vibration of dipoles, especially the water molecules in tissue, and this produces dielectric heat and thermal coagulation around the electrode. One study involving 288 HCC patients who were treated by microwave ablation found that their 1-, 3-, and 5-year survival rates were 92%, 72%, and 51%, respectively[9].

(3) RFA versus microwave ablation

A comparison of the efficacies of microwave ablation and RFA at treating HCC at a single center found that the survival rate was higher in 136 tumors in 99 patients treated by microwave ablation than in 69 tumors in 55 patients treated by RFA, but the difference was not statistically significant[10]. A meta-analysis found that RFA and microwave ablation showed similar efficacies in treating HCC, although microwave ablation was superior to RFA in treating larger lesions[11].

(4) RFA versus cryoablation

A multicenter randomized controlled trial of percutaneous cryoablation versus RFA in HCC found lower local tumor progression in patients treated by cryoablation, especially for lesions with diameters of >3 cm. Both cryoablation and RFA were equally safe and effective, with similar 5-year survival rates[12]. However, a recent meta-analysis[13] found almost equal mortality rates and no significant difference in local tumor progression. That study found that the risks of complications, thrombocytopenia, and renal impairment were higher for cryoablation.

3. Assistive technique for ablation

(1) Real-time image fusion systems

Real-time image fusion systems involve the fusion of two different imaging modalities such as ultrasonography (US), computed tomography, magnetic resonance imaging, and positron- emission tomography. These systems comprise an ultrasound machine, a probe equipped with a magnetic sensor, a transmitter to generate a magnetic field, and a real-time magnetic position detection unit[14]. A fusion imaging system makes it possible to target challenging lesions with confidence and accuracy when performing RFA. There have been many reports of high tumor-targeting success rates when using real-time fusion imaging systems[14-17].

(2) Electromagnetic tracking

The electromagnetic tracking method is the most widely used of the three tracking methods for US-guided hepatic interventions in the fusion imaging technique[18]. The virtual needle tracking system involves an electromagnetic sensor device and utilizes the magnetic field previously used for volume navigation. The path and tip of the needle can be displayed virtually superimposed on the real-time US image. The needle tip is then synchronized with the tracking device by automatic calibration or manual input of the needle's length[19]. In cases where the needle tip appears vague due to the presence of fatty or coarse surrounding liver tissue, or it being deep inside the liver, this technique is advantageous for puncturing and ablating the HCC. There is also an advantage of being able to ablate large tumors by employing multiple needle punctures.

(3) Contrast-enhanced US

Some studies have demonstrated that using a contrast agent during RFA improves the accuracy in detecting and targeting HCC[20-22]. The efficacy of these agents depends on the different ways in which sound waves are reflected from interfaces between substances. Commercially available contrast agents include gas-filled microbubbles, which are administered intravenously into the systemic circulation. Sulfur hexafluoride microbubbles (SonoVue®) and perfluorocarbon microbubbles (Sonazoid®) are widely used as second-generation contrast agents. Contrast-enhanced ultrasonography (CEUS) with Sonazoid was found to increase the detectability of HCC from 83.5% to 93.2%[22], and additionally the nodules detected by CEUS were positively correlated with the serum albumin concentration[22].

(4) Artificial material infusion

Artificial ascites or pleural effusion is useful when a tumor is close to major structures, such as the diaphragm or gastrointestinal tract, in order to avoid thermal injury of the adjacent organ. Furthermore, the infusion of artificial material during RFA helps to decrease the risk of incomplete treatment of a tumor resulting from poor visibility in sonography[23-25] According to a recent review article, the technique of artificial ascites has a high success rate (>90%) without severe adverse events such as intraperitoneal hemorrhage or gastrointestinal perforation, while the complete ablation rate or local tumor progression rate remains satisfactory for difficult-to-ablate HCCs[26].

4. Combination therapies with RFA

(1) RFA plus lyso-thermosensitive liposomal doxorubicin

Lyso-thermosensitive liposomal doxorubicin (LTLD; Thermodox®) is a thermally sensitive liposomal doxorubicin formulation that can be administered intravenously and rapidly releases its drug content when heated to a specific temperature. When used during RFA, LTLD releases its doxorubicin into the vasculature around the zone of ablation-induced tumor cell necrosis, thereby killing micrometastases in the ablation margin[27]. Because tumors have a leaky vasculature and vessels in tumors become more permeable when heated, LTLD can accumulate around the target tumor and release greater amounts of doxorubicin. This may reduce recurrence and be more effective than thermal ablation alone.

(2) RFA plus transarterial chemoembolization

Combination treatment of transarterial chemoembolization (TACE) with RFA has shown more promising results than RFA treatment alone in many studies[28-30]. A recent meta-analysis found that RFA plus TACE was associated with significant advantages in terms of the recurrence-free survival, overall survival, and efficacy, especially when treating intermediate and large-sized HCCs or younger patients with HCCs[31]. The synergy between RFA and TACE has been attributed to occlusion of the hepatic arterial flow by embolization reducing the cooling effects of hepatic blood flow on thermal coagulation and to the gelatin sponge particles used in TACE filling the peripheral portal vein around the tumor. Moreover, TACE can treat undetected satellite lesions surrounding the zone of RFA-induced necrosis.

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DAY 2: Friday, June 17, 2016 (13:10-14:10) WEST TOWER Room F

KLTS Coordinator Session

Chairs : Hea Seon Ha (Asan Medical Center)
Bok Nyeo Kim (Samsung Medical Center)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Preoperative Evaluation of Living Donor Candidate for Liver Transplantation

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The downside of living donor liver transplantation, of course, is the risk to the healthy donor. For the donor safety, preoperative evaluation of donor is important and it should be included psychosocial and ethical issues as well as medical suitability. Here, we introduce a preoperative evaluation of living donor candidate for liver transplantation. Since 2011 our institution`s protocol was introduced, this three-step evaluation protocol have been used in our center (Fig.1). At Step1, the medical examination of candidate for donor by interview includes the medical history, psychosocial circumstance and age; usually 16-60 years. The relationship between the recipient and donor should be within the third degree of consanguinity or an intense emotional relationship judged by ethical board of local committee. At Step 2, potential donor undergoes tests two phase medical evaluation, ethical evaluation and document process. First phase medical evaluation includes basic blood and urine profile, Liver CT scan for graft/remnant volume of liver, ECG and chest X-ray. Second phase medical evaluation includes viral and neoplastic disease and imaging studies, especially primovist MRI and MRCP, for anatomy and quality of the liver include the degree of fatty change. If necessary, the invasive procedures including liver biopsy and additional consultations required to investigate the potential problems discovered during phases 1 and 2 are done. At Step 3, the multidisciplinary team discuss about donor and decide the donation. A preoperative liver biopsy was applied to the moderate steatosis from imaging studies. The presence of mild systemic diseases (e.g., well-controlled hypertension or diabetes) cannot be a contraindication in our protocol. The donors are disciplined to quit smoking and drinking. The remnant liver volume ≥ 30% of the whole liver is recommended. If macrovesicular steatosis is ≥ 10%, we do liver biopsy and recommend diet control. Donors with a GRWR > 0.8% were generally accepted. Usually minimal anantomical variation of the liver has been accepted. Only candidate who passed these all examination, can be a donor for liver transplantation. This detailed evaluation undoubtedly play a role in our successful living donor liver transplantation program, and there was no donor mortality and the overall donor morbidity was < 6.0%, including 0.9% of major complications (> grade III). In conclusion, meticulous donor evaluation is important for the successful LDLT.

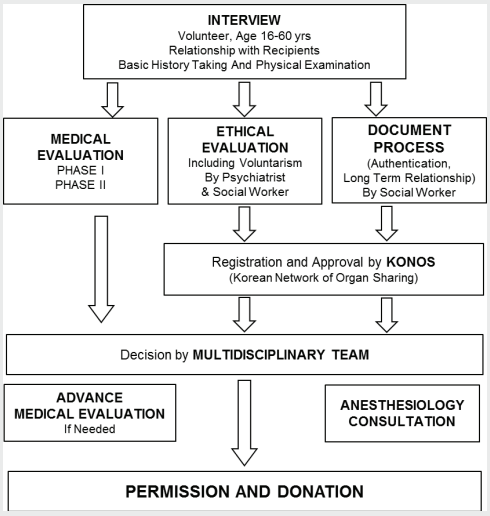

Figure 1. Three-step evaluation protocol of the live donor in SNUH

Education and Counselling for Living Donor for Liver Transplantation
생체 간 공여자를 위한 상담 및 교육

Sunyoung Son

Gangnam Severance Hospital, Korea

간이식은 말기 간질환으로 치료가 불가능한 상태의 환자에게 타인의 간으로 대치하는 수술방법으로 이는 환자의 생명연장 뿐 아니라 삶의 질 증진에도 긍정적인 영향을 미치면서 현재에는 가장 확실한 치료 방법으로 그 입지를 굳혀 가고 있다.[1] 이런 간이식은 장기기증을 뇌사자로부터 받게 되는 뇌사자 간이식과 생체부분 간이식으로 구별되며, 간이식을 필요로 하는 간질환자는 증가하고 있으나 이를 위한 뇌사자 간 공여자의 수가 절대적으로 부족하여 대안으로 생체부분 간이식의 빈도는 빠르게 증가하고 있고, 질병관리본부 장기이식관리센터의 통계연보에 따르면 2000년 171건 이었던 생체부분 간이식은 2014년 858건으로 증가하였으며, 2014년 한해 시행된 간 이식의 1,262건 중 68.0%를 차지하며 증가가 전망되고 있다. 생체부분 간이식이 활발해 지면서 많은 연구가 이루어지며, 간 공여자의 안전 및 신체적 회복, 합병증 예방을 위해 많은 노력을 기울이고 있지만,[2] 아직까지도 많은 연구와 관심은 간 이식 수혜자 중심의 삶의 질, 스트레스, 적응능력과 향상에 초점되어 있으며, 간 공여자의 문제는 간과되어 신체적 문제와 합병증에만 초점되어 있다.[3]

공여자를 대상으로 한 연구 결과 단순한 간 기능회복 뿐만이 아닌 신체 기능 회복 및 삶의 질을 평가한 결과 공여자들은 수술 전 보다 낮은 신체기능 및 삶의 질을 보였으며, 정보 부족으로 인한 간 공여자의 교육 요구도와 정서적인 어려움이 확인되어,[4][5] 최근 진행된 연구들에서 공여자를 위한 상담 및 교육 프로그램을 활성화해야 한다는 보고들이 나오고 있으나, 실제적으로 대부분의 간이식을 시행하고 있는 많은 의료기관에서 간 공여자를 대상으로 수술과정, 수술 전후 관리, 간 공여 후 생길 수 있는 문제와 정서적 관리 등에 대한 포괄적인 교육 및 상담 프로그램의 진행이 적극적으로 이루어지지 않고 있는 상태이다.[6] 간 공여자들 대상 교육 요구도를 확인한 연구 결과에서도 간 공여자들은 간 공여 수술 관련, 간 공여 후 일상생활 관리, 간 공여 후 정서관리, 간 공여 후 사회생활 관리 순의 내용에 대한 교육요구를 보였으며,[7] 간 공여자의 경험을 확인한 연구결과 신체의 불완전한 회복으로 인한 신체적 어려움과 심리 정신적인 양가감정, 사회 경제적인 어려움, 회복시기의 지연 등의 어려움을 겪고 있음을 확인하며 간 공여자를 위하여 장기기증 전후로 심리 정신적 상담의 필요성을 제시하였다.[5]

생체 간이식의 놀라운 업적에도 불구하고 생체 간 공여자를 위한 의료의 현 실태는 특화된 중재의 필요성만 확인된 채 실제적인 적용이 이루어지지 않고 있는 상황이다. 예기치 않은 부작용과 합병증을 겪게 되거나, 수혜자의 경과 악화 혹은 죽음을 지켜볼 수도 있는 공여자들에게 그들의 신체 및 정신건강과 회복 및 적응을 위하여 할 수 있는 것이 무엇인지를 고민해 봐야 할 이 시점에서 관여된 전문인들이 생체 장기기증자의 건강증진을 위하여 교육 및 상담의 활성화에 대한 책임과 의무를 다해야 할 때임을 밝히고 싶다.

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Preparation for Emergency Liver Transplantation

Ji Yeon Park

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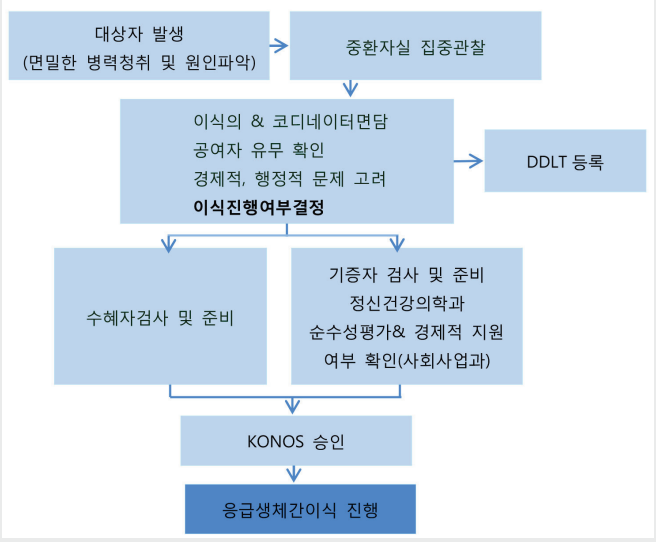
응급 간이식의 준비

박 지 연

서울성모병원 장기이식센터

급성 간부전(Acute liver failure)이란 기저질환이 없는 사람에서 간손상의 증상발현으로부터 26주 이내에 간 기증의 급격한 저하와 함께 혈액 응고 및 의식 변화가 나타나는 상태를 의미한다. 또한 만성질환을 가진 환자에서 감염이나 급성 간손상과 같은 선행 인자에 의해 급성 악화 소견을 보이는 환자군을 acute-on-chronic liver failure (ACLF)로 정의한다.
급성 간부전으로 진행되는 경우 문진을 통해 간부전의 원인을 파악하는 것이 중요하고 임상 증상에 따라 중환자실에서의 집중관리가 필요하며 동시에 응급 간이식에 대한 준비가 필요하다. 급성 간부전은 사망률이 매우 높아 응급 간이식이 수일 내에 이루어지지 않으면 뇌부종, 전신감염의 합병증으로 인한 사망 위험이 매우 높으며, 이식 전 환자의 상태는 이식 후 환자 생존율에도 많은 영향을 미친다. 응급간이식이 필요한 경우, 적절한 생체 공여자가 없다면 응급도의 기준에 따라 국립장기이식관리센터(KONOS)를 통해 응급도의 기준에 따라 뇌사자 간이식 대기자 명단에 등록하고 응급등급1인 경우 우선적 배분을 받게 된다. 그러나 뇌사 공여자가 부족한 국내 현실상 생체이식으로 진행하는 경우가 많아 신속하게 기증자의 의학적인 검사를 진행하고 정신건강의학과와 사회사업팀의 면담을 통하여 기증자로서 적합한 경우에 국립장기이식관리센터의 응급 생체 간이식에 대한 승인을 받고 수술을 진행하게 된다.
코디네이터는 환자 및 가족에게 수혜자의 검사 및 진행절차, 간이식 비용, 수술방법, 간이식 후 합병증, 간이식 후 관리, 재원기간, 수술 생존율등의 전반적인 사항과 기증자의 검사종류 및 행정적 승인절차, 입원기간, 회복기간, 간 기증 후 관리 및 주의사항 등에 대한 정보를 제공하여 응급으로 진행하는 간이식의 불안감을 최소화 할 수 있도록 돕는다. 또한 간이식과 관련되는 여러 부서와 원활하게 의사소통을 하여 성공적으로 이식이 이루어 질 수 있도록 조정해야 한다.



Immuno Suppression after Liver Transplantation

Jeong Hee Kang

Pusan National University Yang-san Hospital, Korea

이식의 역사를 살펴보면 면역학적 거부반응에 대한 치료제의 개발 및 발전 또한 이식의 역사와 함께 이루어졌다고 보여진다. 하지만 오늘날에도 완전하게 이해되지 못하는 이식 거부반응은 계속 존재하고 있으며 이는 장기이식 후 환자 관리에 있어 풀어나가야 할 영원한 과제이다.

면역억제제의 개발은 1960년대, 1970-80년대, 1990년대 이후로 나누어 살펴 볼 수 있고, 1976년 Cyclosporine A가 개발되면서 이식의 역사에 큰 획을 그었다. 많은 임상 연구 결과를 통해 과거에 비해 현재 면역억제제 치료 효과는 매우 긍정적이다. 우리나라에서 간이식을 시행받는 환자 중 기저질환이 간암인 경우는 매년 증가하고 있으며(국립장기이식센터, 2015), 면역억제제 사용으로 인한 종양발생증가 및 종양재발의 위험은 충분히 고민해야 될 문제로 떠올랐다. 최근에는 면역억제제의 병행요법, Calcineurin inhibitor(CNI) 제제 사용의 최소화와 함께 새로운 약제들이 개발되어 사용되고 있으며, 기존 면역억제요법의 부작용을 최소화 하기 위한 면역억제 치료방법들이 고안되고 있다. 또한 새롭게 선보여진 항종양 효과를 가진 면역억제제에 대해서는 현재에도 약물의 효과에 대한 임상연구가 활발하게 이루어지고 있다. 향후 더 많은 임상 연구를 통해 신뢰있는 결과를 도출하여 면역억제 치료에 적용된다면 장기이식은 더욱 안정적이고 효과적인 치료방법 중 하나로 자라잡을 것이다.

DAY 3: Saturday, June 18, 2016 (08:30-09:50) WEST TOWER Room AB

Symposium 2

Pros and Cons of LC-Controversial Issues

Chairs : Samuel Lee (Univ. of Calgary)
Sung Won Cho (Ajou Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Nonselective Beta Blocker: Hemodynamic Effects vs. Non-hemodynamic Effects

Moon Young Kim

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Nonselective blocker (NSBB) has been only one medication which was recommended for the control of portal hypertension (PHT) and there have been much data that shows the reduction by NSBB of variceal hemorrhage risk in primary and secondary prophylaxis in patients with cirrhosis. In addition, some data has suggested that reduction in portal pressure might also be beneficial for other outcomes, such as ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, and overall survival.

The hemodynamic effect of NSBB has been absolutely accepted as the main mechanism for the beneficial effects in PHT: β-1 cardiac receptor blockade results in lowered portal venous inflow through mechanisms of cardiac output reduction, whereas β-2 vascular receptor blockade leads to splanchnic arteriolar vasoconstriction and a reduction of portal-collateral (variceal) blood flow. Hemodynamic responders in hepatic venous pressure gradient (HVPG) after NSBB therapy are considered unlikely to experience variceal bleeding/rebleeding.

However, a large proportion of hemodynamic non-responders also does not bleed or rebleed and seem to experience a protective effect from NSBB. The previous much data have already shown that about half portion of non-responder to NSBB did not rebleed and about 40% patients were hemodynamic non-responder among patient who did not rebleed in the long term follow up. It is very important finding because it means NSBB has another effect in variceal bleeding prevention beyond hemodynmic effect[1]. Hence, according to a response to NSBBs, patients with cirrhosis and PHT have been classified into "white," hemodynamic responders who look protected against the risk of bleeding, "black," hemodynamic non-responders who will bleed/ rebleed during the treatment, and "gray," hemodynamic non-responders who are unlikely to bleed/rebleed during treatment[1]. Although the mechanisms underlying the gray zone are not fully understood, the evidences show that both risk and prognosis of variceal hemorrhageg in PHT are not the mere consequence of hemodynamic changes in the portal area, but non-hemodynamic protective effect of NSBB which may be depend on multiple biological variables including a reduction of sympathetic tone and bacterial translocation (BT) is also important[2].

Decreased intestinal motility, increased intestinal permeability, and bacterial overgrowth frequently occur in cirrhosis and induce potentially important clinical implications in the domain of BT[3]. The severity of PHT estimated by HVPG, correlates with the degree of GI permeability and the onset of BT not only in decompensated but also in compensated cirrhosis[4]. BT makes the clinical situation of circulating potentially pathogenic byproducts of bacterial origin, like lipopolysaccharide (LPS), that in the animal model proved to aggravate pathophysiological PHT by the worsening of arterial mesenteric vasodilatation as a consequence of a hyporesponse to vasoconstrictors[5, 6]. BT exerts relaxing effects on peripheral vascular resistance that result in hyperdynamic circulation, however, in contrast, selective intestinal decontamination with poorly absorbable antibiotics resulted in hemodynamic improvements in patients with cirrhosis and PHT[7].

NSBB also shows similar data with selective decontamination with antibiotics in BT. In a recent study, NSBB treatment showed decrease of gastroduodenal/ intestinal permeability and reduced bacterial translocation and it partially contributed to a reduced risk of variceal bleeding, independent of their hemodynamic effects on portal pressure[4]. In another recent

study, ongoing treatment with NSBB in cirrhosis seems to be safe and reduces the mortality in ACLF condition through the control of sympathetic tone and BT and reduction of the severity of systemic inflammation[8].

Recently, NSBB has been forced into corner in the clinical practice and are in danger of losing its unique position in a PHT and cirrhosis management. However we still do not have enough data for the diverse action mechanism of NSBB in a various/heterogeneous clinical situation. Non-hemodynamic effect of NSBB should not be overlooked and we need to wait for more data before close the 'Window'.

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Scoring Systems for Alcoholic Hepatitis

Patrick S. Kamath

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Alcoholic hepatitis is associated with a high risk of short-term mortality, between 30-50% at 3 months. Alcoholic hepatitis has been associated with multi-organ failure when superimposed on chronic liver disease, a condition more recently termed, "acute on chronic liver failure". Management of the patient with alcoholic hepatitis requires intensive care in those with multiple organ failure; specific treatments aimed at reversing the hepatic injury; and interventions towards alcohol rehabilitation. Corticosteroids improve survival at 28 days, though the magnitude of benefit may not be as large as previously believed. Among those patients who respond to steroids, complete abstinence from alcohol is associated with improved survival at one year. No medical therapy alone is associated with improved survival beyond 6 months, and liver transplantation remains the best option for patients with liver failure who are rehabilitated from alcohol abuse. There is a subset of patients in whom all interventions, either medical or psychosocial, are futile.

In patients with alcoholic hepatitis, the risk for mortality is related to severity of liver disease, the attending complications of infection and multiple-organ failure, inflammatory response, histology, risk for continued alcohol abuse, and perhaps genetic polymorphisms. Identifying whether the course of implemented therapy is having the intended effect is also critical so that the therapy and its inherent toxicities can be obviated if a benefit is unlikely to be conferred. Such is the example with corticosteroid therapy whereby initial studies showed that a lack of improvement in bilirubin after one week of therapy indicated futility. There is, therefore, the need for accurate risk scores to stratify patients for mortality at both baseline state and at interval times after initiation of therapy.

Mathurin and colleagues combined static scores (MDF, MELD and ABIC) with a dynamic score (Lille) to determine which combination had the best prognostic value. They concluded that the MELD + Lille combination was significantly better than the MDF + Lille, or ABIC + Lille score in predicting patient survival.

Anticoagulation: Do or Avoid?

Erica Villa

University of Modena and Reggio Emilia, Italy

Cirrhosis traditionally has been considered a hypocoagulable state; recently it has become clear that is a rather composite condition in which liver synthetic deficit rebalances coagulation by reducing both procoagulant and anticoagulant factors. This leads to an unstable haemostatic balance with a lower threshold for either thrombosis or bleeding. In compensated cirrhosis, this balance, although unstable, is sufficient and no special measures (blood transfusions, FFP, platelets) are required, even for patients undergoing invasive procedures. Accurate evaluation of coagulative profile (e.g. with TEG instead than with routine coagulative tests), leads to significantly lower use of blood products without additional risks for the patients (Hepatology. 2016 Feb;63(2):566-73. doi: 10.1002/hep.28148. Epub 2015 Dec 9). Indeed, apart from the gastrointestinal tract, the occurrence of spontaneous and procedure-related bleeding elsewhere in the body, whilst not uncommon, is less than ir could be expected.
During the course of cirrhosis, however, in parallel with progression of severity of disease, thrombophilic events, like portal vein thrombosis (PVT), become a frequent event occurring up to 40% of patients with liver cirrhosis.
LMWH has been shown to be safe and effective in the treatment of PVT in cirrhotic patients (Eur J Gastroenterol Hepatol. 2015 Aug;27(8):914-9. doi: 10.1097/MEG. 0000000000000351.
PVT causes deterioration of the clinical course, portal hypertensive complication and post-transplant mortality. Pathogenesis of PVT includes both local alterations, like blood flow reduction and endothelial activation, and systemic derangements. Systemic prohemostatic alteration include high von Willebrand factor, low ADAMTS 13, low levels of anticoagulants (antithrombin, protein C–S) and increase in procoagulants like factor VIII.
We have previously shown that Low Molecular Weight Heparin (LMWH) such as Enoxaparin is safe and effective both in treatment and prevention of PVT. Furthermore, patients in prophylaxis with enoxaparin showed a lower rate of decompensation and a better survival without bleeding complications. (Gastroenterology. 2012 Nov;143(5):1253-60.e1-4. doi: 10.1053/j.gastro.2012.07.018. Epub 2012 Jul 20). In such patients circulating bacterial DNA, endotoxemia and markers of inflammation were attenuated compared to controls. These results therefore suggest a possible connection between enoxaparin and decrease of endotoxemia and reduction of portal hypertension. Enoxaparin was safe and no significant side effects were encountered. We have also subsequently shown that Enoxaparin treatment does not increase bleeding risk in patients undergoing invasive or non-invasive endoscopic procedures performed while on Enoxaparin (ILC2016-RS-3560).
On the whole, there is sufficient evidence to support the use of LMWH in patients with advanced cirrhotic disease to prevent not only PVT but also progression of disease and decompensation. It is still a matter of debate if longer duration of Enoxaparin treatment could be even more beneficial. In the Gastro 2012 study, the favourable effect of Enoxaparin was lost few months after stopping therapy. This is understandable if one thinks that Enoxaparin likely acts by modifying microcirculation both at the intestinal and hepatic level and that this effect is bound strictly associated with drug administration.
Confirmatory studies are on their way.

Albumin: New Roles beyond Volume Expander

Samuel S. Lee

University of Calgary, Calgary, Canada

Albumin is a 65-70kDa protein that accounts for approximately half the total plasma protein content in humans. For many years, it was thought that its only two functions were to bind to various substances so they could be transported or stabilized, and to provide a major part of the plasma oncotic pressure, also called colloid osmotic pressure.

Research over the past 3 decades has established numerous other essential roles of albumin. Moreover, it has been found to improve outcomes not just in liver disease but a number of other pathologic conditions including stroke, sepsis, acute lung injury and subarachnoid hemorrhage. In liver disease, albumin has been found to be useful to help treat or manage spontaneous bacterial peritonitis, hepatorenal syndrome, resistant ascites, post-paracentesis circulatory dysfunction and hyponatremia.

The other mechanisms of action besides its colloid osmotic effect can be grouped into several categories. These include substance detoxification/stabilization, metal binding, cell stabilization and immune/anti-inflammatory effects. At the cellular level, it mediates many of these effects due to its small size, binding domains, charge and ability to enter a variety of cells. It thus subserves several important physiological functions in health, but in cirrhosis, several of these functions have been demonstrated to be impaired.

Specific examples of these normal beneficial cellular effects include reduction of oxidative stress and immune stabilizing. Albumin enters endothelial cells and in animal models of liver disease, has been shown to reduce the deleterious effects of LPS and endotoxin primarily through a TLR-mediated effect. It also improves endothelial function as judged by markers such as Von Willebrand Factor production. It can also improve neutrophil function to reduce infection risk in cirrhosis. In the kidney, it appears to restore renal blood flow autoregulation by an unclear mechanism. but one that seems to be largely independent of its effect as a volume expander. Several studies have demonstrated reduction of oxidative stress in the liver and vasculature by albumin.

The function of numerous other organ systems in cirrhosis is known to be altered, and dysfunctional albumin may play roles in those systems' dysfunction.

The role of albumin in the blood vessels and vasculature has been studied but possible effects in the cirrhotic lung and heart have not yet been clarified. These areas are fertile ground for future research.

DAY 2: Saturday, June 18, 2016 (13:20-13:50) WEST TOWER ROOM A

Special Lecture 2.

Chair : Kwan Soo Byun (Korea Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Hepatitis C Virus: Next Generation of DAAs

Mark Sulkowski

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Johns Hopkins University School of Medicine
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In the current era, multiple HCV treatment regimens have been developed that are interferon-free and deliver high rates of HCV cure (> 95%) in most patient populations with treatment durations in the range of 12 weeks. In the context, the question can and should be asked: Is there a medical need for a next generation of DAAs. In short, the answer is that novel drugs and drug regimens are needed for certain patient populations including 1) Person who failed to achieve HCV cure with current DAAs need "salvage" regimens that can overcome HCV drug resistance associated variants (RAVs); 2) HCV genotype 3 for whom the treatment options are limited; 3) Persons for whom ribavirin is still recommended including those with HCV genotype 2 and some patients with cirrhosis.

HCV NS3 Protease inhibitors. The first wave of HCV protease inhibitors – telaprevir, boceprevir and simeprevir – are not pangenotypic, lacking potent antiviral activity against HCV genotype 3. There are two protease inhibitors in phase 3 clinical trials that are once daily, potent, pangenotypic drugs: Voxilaprevir (VOX, GS-9857) and ABT-493. Voxilaprevir is being developed as a fixed-dose combination tablet including sofosbuvir and velpatasvir (a pangenotypic NS5A inhibitor). ABT-493 is being developed as a fixed-dose combination tablet including ABT-530 (a pangenotypic NS5A inhibitor). Both regimens are currently being evaluated in phase 3 clinical trials for treatment durations of 8 and 12 weeks in persons with all HCV genotypes and in those who failed DAA regimens.

HCV NS5A inhibitors. Similar to protease inhibitors, many of the first wave of NS5A inhibitors lacked activity against HCV genotype 2 and 3 infection (the exception is daclatasvir). Velpatasvir is pangenotypic and has competed phase 3 trials in combination with sofosbuvir. The fixed-dose combination tablet given for a duration of 12 weeks led to HCV cure in > 99% of persons with HCV genotype 1, 2, 4, 5 and 6 infection and 95% of those with HCV genotype 3. This regimen is expected to be approved in the US and Europe in 2016. Other pangenotypic protease inhibitors in development include MK-8408 and the above-referenced ABT-530. While studies are ongoing, ABT-530 appears to be among the most active NS5A inhibitors against NS5A RAVs are position 93.

HCV NS5B inhibitors. To date, sofosbuvir is the only approved nucleotide analogue NS5B inhibitor. Other DAAs in this class have been discontinued due to drug toxicity. In this context, MK3682 and AL-335 are currently in phase 2 clinical trials. MK3682 is being developed in combination with grazoprevir (NS3 protease inhibitor) and MK-8408 as a fixed dose combination tablet for the treatment of all HCV genotypes. Similarly, AL-335 is being tested in combination of AL-335, Odalasvir (NS5A inhibitor), and Simeprevir for the treatment of Genotype 1 chronic HCV infection.

DAY 3: Saturday, June 18, 2016 (13:50-15:10) WEST TOWER Room AB

Special Interest Group Symposium 2

Cirrhosis with Portal Hypertension : Liver-Heart-Kidney Axis, from Portal Hypertension to Hyperdynamic Circulatory Syndrome

Chairs : Joo Hyun Sohn (Hanyang Univ.)
Soon Koo Baik (Yonsei Univ. Wonju)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

The Diagnosis of Acute Kidney Injury in Cirrhosis: The Reasonable Cut-off Serum Creatinine Value

Florence Wong

University of Toronto, Toronto, Canada

Traditionally, the diagnosis of acute renal failure in cirrhosis is made using the conventional criterion of a 50% increase in serum creatinine (SCr) with the final SCr reaching ≥1.5 mg/dL. The recent recognition that even small increases in SCr irrespective of the final SCr level can have a negative impact on survival in cirrhosis has led to refinement of the definition of acute renal failure, or more commonly known as acute kidney injury (AKI) nowadays. The severity of AKI is then defined by different stages. Thus stage 1 AKI represents a small but acute increase in SCr by 0.3 mg/dL or 26.4μmol/L in < 48 hours, or 1.5-2 times increase in SCr from baseline. Stages 2 and 3 AKI represent 2.1-3 times and >3 times of increase in SCr respectively, without a cut-off SCr threshold. There followed a flurry of studies that used this new definition of AKI and many reported the utility of the new definition and staging system in predicting prognosis of cirrhotic patients with AKI. However, many were not convinced that this new system adds any information to what we already know about the prognosis of advanced cirrhosis. In 2 recent articles, which evaluated the impact of AKI on short-term mortality in patients with decompensated cirrhosis admitted to the hospital for various reasons, both the new AKI criteria with the conventional criteria for the diagnosis of AKI were applied. The first study reported that patients with stage 1 AKI and a peak SCr of ≤1.5 mg/dL had a very good survival, similar to that of non-AKI patients. Therefore, a threshold of SCr of 1.5 mg/dL should be retained in the determination of prognosis for these patients. The second study found that the conventional diagnostic criteria with a cut-off SCr of 1.5 mg/dL was better than the new AKI criteria in the prediction of survival. Furthermore, a SCr of ≥1.5 mg/dL was able to predict progression of AKI. However, a larger study of infected cirrhotic patients found that the new AKI diagnostic criteria were accurate in predicting survival. These desperate results therefore fuel an ongoing debate as to whether the conventional or the new AKI diagnostic criteria are better in the prognostication of these cirrhotic patients. In advocating for a cut-off SCr of 1.5 mg/dL, there is a concern that treatment for AKI may be delayed till the threshold is reached. Conversely, if a threshold SCr for the diagnosis of AKI is not set, patients may start expensive pharmacological treatment for AKI when it may not be required. Therefore, the International Ascites Club, in setting a compromise, suggested that the new diagnostic AKI criteria should remain, as there is sufficient evidence to support their application in cirrhosis as accurate. However, pharmacological therapy should not be started until AKI has progressed to at least stage 2. These guidelines will need to be validated in further studies before they can be generally applied to all cirrhotic patients.

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The Current Management of Acute Kidney Injury in Cirrhosis

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간경변에서의 급성간손상의 치료

정 승 원

순천향대학교 서울병원 소화기내과

급성간손상은 간경변증에서 흔히 발생되는 합병증으로 사망률을 증가시킨다. 고전적인 개념의 급성간손상은 혈청 크레아티닌이 기저치에 비해서 50% 이상 증가하여 최종 수치가 1.5 mg/dL를 초과하는 경우로 정의되어 왔으나, 최근 2015년 International Club of Ascites (ICA)에서는 급성간손상의 진단을 48시간 내 혈청 크레아티닌 0.3 mg/dL 이상 상승 또는 이전 7일 이내 기저치로부터 50% 이상 상승한 경우를 새로운 진단기준으로 제시하였다. ICA 에서는 급성간손상을 1-3단계로 분류하여 1단계의 급성간손상에는 신독성이 있는 약물을 끊고, 혈량저하증에는 알부민등을 투여하여 혈장량을 늘리고, 감염시에는 항생제를 투여하며, 이러한 일반적인 치료에도 진행이 되거나 2단계 또는 3단계의 급성간손상에는 먼저 이뇨제를 끊고, 알부민(1 g/kg)을 2일간 투여하고, 여기에도 반응이 없으면 간신증후군의 기준에 해당되는 경우 혈관수축제와 알부민의 병합투여를 추천하였다. 급성간손상의 진단기준과 치료가 새롭게 발표되면서 향후 간신증후군 진단기준에도 변화가 요구되며, 좀 더 신속한 진단과 대처를 통해서 사망률을 줄이고 치료 효과를 높이는 방향으로의 치료가 전망된다.

Renal dysfunction is a common complication of advanced cirrhosis, occurring in approximately 20% of patients admitted to hospital.[1] Almost all of the cases of renal dysfunction are related to acute renal failure, nowadays more commonly known as acute kidney injury (AKI).[1]

Cirrhotics with AKI have poor prognosis with an overall survival rate of 50% at 1 month and 20% at 6 months.[2] In a systematic review of 118 studies evaluating predictors of survival in cirrhosis, high serum creatinine was a powerful predictor of death in decompensated cirrhosis.[3]

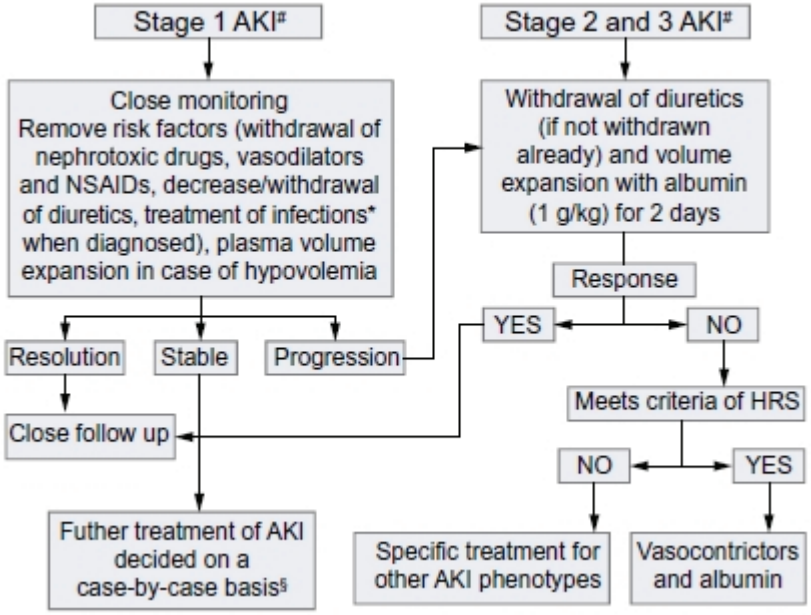
Recently, a new algorithm for the management of AKI in patients with cirrhosis was recommended according to the new international club of ascites (ICA-AKI) diagnostic criteria for AKI (Table 1).[4,5] The algorithm is based on the new staging of AKI (Fig. 1).[4,5]

Table 1. International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis (Adapted from Angeli P, et al. J of Hepatology 2015;62:968-974)[4].

Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or, • A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days		
Staging of AKI	• **Stage 1**: increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline • **Stage 2**: increase in sCr >2-fold to 3-fold from baseline • **Stage 3**: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy		
Progression of AKI	**Progression**	**Regression**	
	Progression of AKI to a higher stage and/or need for RRT	Regression of AKI to a lower stage	
Response to treatment	**No response**	**Partial response**	**Full response**
	No regression of AKI	Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value	Return of sCr to a value within 0.3 mg/dl (26.5 µmol/L) of the baseline value

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.

Figure 1. Proposed algorithm for the management of AKI according to ICA-AKI (Adapted from Angeli P, et al. J of Hepatology 2015;62:968-974)[4].



Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines. #Initial AKI stage is defined as AKI stage at the time of first fulfilment of the AKI criteria. §No global consensus was reached on this point. HRS, hepatorenal syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; sCr, serum creatinine.

Patients with cirrhosis and ascites with initial ICA-AKI stage 1 should be managed as soon as possible with the following measures:

1) Drug : review of all medications (including over the counter (OTC) drugs), diuretics, all potential nephrotoxic drugs, vasodilators or non-steroidal anti-inflammatory drugs (NSAIDs)

2) Hypovolemia : Plasma volume expansion in patients with clinically suspected hypovolaemia (with crystalloids or albumin or blood (in patients who had AKI as a result of gastrointestinal bleeding) according to clinical judgment).

3) Infection : Prompt recognition and early treatment of bacterial infections when diagnosed or strongly suspected. Patients who recovered sCr to a value within 0.3 mg/dL (26.5 lmol/L) of the baseline value should be followed closely for early identification of potential new episodes of AKI (hospitalization period : assessment of sCr every 2–4 days, outpatients period : assessment of sCr at least every 2-4 weeks during the first 6 months after the discharge).[6]

The patients who show the progression of the AKI stage should be treated as patients with ICA-AKI stage 2 and 3. They should be treated with the withdrawal of diuretics, if it had not been previously stopped, as well as infusion of intravenous albumin at the dose of 1 g per kg bodyweight per day for two consecutive days, in order to treat pre-renal AKI and to allow differential diagnosis of AKI. The maximal dose per day of albumin should not exceed 100 g as previously suggested.[7] Patients who do not show response to diuretic withdrawal and plasma volume expansion will require the final diagnosis of the AKI type by differential diagnosis between an hepatorenal syndrome (HRS)-AKI, an intrinsic AKI, and post-renal-AKI.

Diagnostic criteria of HRS-AKI type in patients with cirrhosis are as follows[4,5]; 1) Diagnosis of cirrhosis and ascites, 2) Diagnosis of AKI according to ICA-AKI criteria, 3) No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight, 4) Absence of shock, 5) No current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.), 6) No macroscopic signs of structural kidney injury, defined as: absence of proteinuria (> 500 mg/day), absence of microhaematuria (> 50 RBCs per high power field), normal findings on renal ultrasonography.

Patients who meet these criteria may still have renal structural damage like tubular damage. To differentiate HRS from acute tubular necrosis, urine biomarkers of tubular damage, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) interleukin-18 (IL-18), and liver fatty acid-binding protein (L-FABP) can play an important role.

Based on the new ICA-AKI algorithm, when AKI is assessed by an initial stage 2 or 3 or by progression of the initial stage despite general therapeutic measures, patients who meet diagnostic criteria of HRS provided by the previous definition[7] should receive vasoconstrictors and albumin, irrespective of the final value of sCr.

Because the present criteria of type 1 HRS does not allow physicians to start treatment with vasoconstrictors and albumin until the sCr increases to ≥ 2.5 mg/dl, a revision of these criteria is needed. New ICA-AKI algorithm suggests to change the rigid sCr cut-off value of > 2.5 mg/dl to the earlier treatment leading to a better outcome as compared with the current approach.

However, ICA-AKI criteria do not rule out the possibility of renal parenchymal damage.[8] Thus, the new urinary biomarkers are needed in the differential diagnosis of the different types of AKI in patients with cirrhosis. Preliminary results from Europe and the USA showed that the use of NGAL[8] and/or the combination of urinary biomarkers (NGAL, KIM-1, IL-18, L-FABP and albuminuria)[9] may be useful in the differential diagnosis of AKI in patients with cirrhosis.

In conclusion, the current management of AKI in cirrhosis is changing to remove stringent absolute cut-offs for serum creatinine more than 2.5mg/dl as proposed previously for diagnosis of type 1 HRS and to initiate the earlier treatment leading to a better outcome.

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Role of Heart in Refractory Ascites, Acute Kidney Injury and Hepatorenal Syndrome

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Renal dysfunction is one of the dominant extrahepatic conditions invariably associated with the progression of cirrhosis. The entire liver-kidney axis has been intensely studied over the past 5 decades but many questions remain unanswered to date. However, it is well known that as chronic liver disease progresses and worsens, it is accompanied by worsening renal function. In particular, the kidney behaves as if the body is severely volume-depleted, and thus intensely conserves salt and water. The extent of such salt/water retention is mild in the early stages of compensated cirrhosis but gradually increases in rough correlation to increasing liver dysfunction and the onset of endstage decompensated cirrhosis. Thus as liver disease progresses, mild ascites becomes severe or refractory ascites, and the extreme end of the sodium/water retention spectrum can be seen: the conditions of acute kidney injury (AKI) and hepatorenal syndrome (HRS) which are characterized by the most intense salt/water retention of any human disease state, and the elaboration of small amounts of virtually sodium-free urine, or at its extreme, anuria.

For the past half-century, the two theories to explain such renal dysfunction were the 'underfill' and the 'overflow' hypotheses. Over the past 3 decades, the 'peripheral vasodilatation' (PVD) hypothesis, which is actually a modest reworking of the 'underfill' theory, has become the dominant, most widely-accepted theory. The PVD theory contends that the initiating event is widespread peripheral vasodilatation is the initiating event that leads to an underfilled circulation, sensed by the kidney and other organs as 'decreased effective circulating volume'. Thus the kidney conserves salt and water in a futile attempt to defend the circulation. The main factor responsible for the vasodilatation remains unsettled: nitric oxide excess has been suggested but note entirely supported by experimental evidence. A general imbalance of the vasodilator:vasoconstrictor systems in favor of the former, has generally been shown.

Until our work on cirrhotic cardiomyopathy starting in 1990, all previous experimental studies in this topic had exclusively focused on the peripheral vasculature in cirrhosis. However, just on first principles alone, it is clear that the pump at the center of the blood circulation must play a role in the genesis of a decreased effective circulation. In other words, whether or not the vessels are dilated, in order for the circulation to be ineffective, pump function must also be abnormal in some way: either the vessels are normal conduits and the pump is inadequate, or the vessels are dilated and pump function is inadequately compensating for the dilated conduits.

This presentation will review clinical and experimental work over the past 2 decades that strongly suggests that inadequate pump function, otherwise called cirrhotic cardiomyopathy, is a major contributor to the key concept of decreased effective circulating volume that lies at the heart* of the peripheral vasodilatation hypothesis. (* pun intended)

The Liver in Cardiac Disease

Patrick S. Kamath

Mayo Clinic College of Medicine, USA

There are approximately one million adult patients with congenital heart disease (CHD) in the United States and the number is increasing. Hepatic complications are common and may occur secondary to persistent chronic passive venous congestion or decreased cardiac output due to the underlying cardiac disease, or as a result of palliative cardiac surgical procedures performed in infancy or childhood; transfusion or drug related hepatitis may also occur. The unique physiology of Fontan circulation is particularly prone to development of hepatic complications and is in part related to the duration of the Fontan procedure. Liver biochemical test abnormalities may be related to cardiac failure, due to intrinsic liver disease, secondary to palliative interventions, or drug-related. Ascites, hemorrhage from gastro-esophageal varices, portal vein thrombosis, and rarely, hepatocellular carcinoma may also occur. Abnormalities such as hypervascular nodules are often seen; in the presence of cirrhosis surveillance for hepatocellular carcinoma is necessary. Judicious perioperative support is required when cardiac surgery is performed in patients with advanced hepatic disease. Traditional models for liver disease staging may not fully capture the severity of disease in patients with CHD. The effectiveness or safety of isolated liver transplantation in patients with significant CHD is limited in adults; combined heart-liver transplantation may be required in those with decompensated liver disease or hepatocellular carcinoma, but experience is limited in the presence of significant CHD. The long term sequelae of many reparative cardiac surgical procedures are not yet fully realized, and understanding the unique and diverse hepatic associations and the role for early cardiac transplantation in this population is critical. As this population continues to grow and age, consideration should be given to develop consensus guidelines for a multidisciplinary approach to optimize management of this vulnerable population.

DAY 3: Saturday, June 18, 2016 (08:30-09:50) WEST TOWER Room C

KHPBS-KLTS Joint Symposium

How Can We Overcome Complicated Portal Vein?

Chairs : Dong Goo Kim (The Catholic Univ. of Korea)
Jae-Won Joh (Sungkyunkwan Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Indication or Contraindication of Liver Transplantation in Patient with Portal Vein Thrombosis

Nam-Joon Yi

Department of Surgery, Seoul National Univ. College of Medicine, Seoul, Korea

Portal vein thrombosis (PVT) occurs in approximately 2%-26% of the patients awaiting liver transplantation (LT) and is no longer an absolute contraindication for LT. Nearly half of PVT cases are accidentally found during the LT procedure. The most important risk factor for PVT development in cirrhosis may be the severity of liver disease and reduced portal blood flow. Whether other inherited or acquired coagulation disorders also play a role is not yet clear. The development of PVT may have no effect on the liver disease progression, especially when it is nonocclusive.

PVT may not increase the risk of wait-list mortality, but it is a risk factor for poor early post-LT mortality. Anticoagulation and TIPS are 2 major treatment strategies for patients with PVT on the waiting list. The complete recanalization rate after anticoagulation is approximately 40%. The role of TIPS to maintain PV patency for LT as the primary indication has been reported, but the safety and efficacy should be further evaluated. PVT extension and degree may determine the surgical technique to be used during LT.

If a conventional end-to-end anastomotic technique is used, there is not a major impact on post-LT survival. However, the problem is the extensive thrombosis from portal to splachnic venous thrombosis (SVT) (Fig.1) PVT is more commonly managed by endovenous thrombectomy (Fig.1. A ,B), while SVT requires more complex technical expedients (Fig. 1. C, D). Several surgical techniques have been proposed, i.e., extensive eversion thrombectomy, anastomosis to collateral vein, reno-portal anastomosis, cavo-portal hemi-transposition, portal-arterialization, and combined Liver-Intestinal transplantation. In order to achieve satisfactory outcomes, careful planning of the surgical strategy is mandatory. The excellent results that are obtained nowadays confirm that, even extended, SVT is no longer an absolute contraindication for LT. Patients with advanced PVT may preferentially be referred to specialized centers, in which complex vascular approaches and even multivisceral transplantation are performed.

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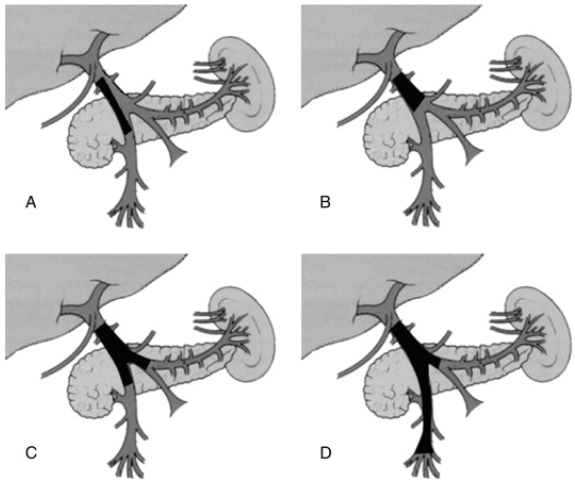

Figure1. Stratification of PVT
A (Grade I): < 50% thrombosis of portal vein with or without minimal extension into the superior mesenteric vein (SMV); B (Grade II): >50% occlusion of the portal vein, including total occlusions, with or without minimal extension into the SMV; C (Grade III): complete thrombosis of both portal vein and proximal SMV, distal SMV is patent; D (Grade IV): complete thrombosis of the portal vein and proximal as well as distal SMV.

Anatomical Reconstruction

Gyu-Seong Choi

Sungkyunkwan University, Korea

How to Overcome Complicated Portal Vein Thrombosis? Extra-anatomic Bypass

Deok-Bog Moon, Sung-Gyu Lee, Chul-Soo Ahn, Gil-Chun Park, Shin Hwang, Ki-Hun Kim, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung

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

When portal vein is severely thrombosed or obliterated, we can not use native portal vein as a portal inflow. Under that situation, we have to use another routes to reestablish the portal flow at the time of liver transplantation. In contrast to deceased donor liver transplantation, muti-visceral organ transplantation or porto-caval hemitransposition are not solutions for severe complicated portal vein. Under those situation, we have used superior mesenteric vein, left renal vein, inferior mesenteric vein, pericholedochal varix, coronary vein, gonadal vein, etc. for portal flow reconstgruction. In case of large splenorenal shunt, we performed 13 cases renoportal anastomosis. In case of large choledochal varix, we performed 6 cases Choledochal varix-portal anastomosis. Otherwise, we performed various type of mesenteric-portal anastomosis in 9 cases. We will introduce how to select portal inflow and our results and lessons learned from our cases.

Intervention for Complicated Portal Vein

Gi-Young Ko

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Various interventional procedures, including balloon angioplasty, stent placement, thrombolysis, mechanical or aspiration thrombectomy, and variceal embolization may help to obtain brisk portal venous inflow during or after liver transplantation. These interventional procedures are usually performed via a percutaneous transhepatic route, however trans-mesenteric venous access during liver transplantation is another valuable route to do interventional procedures.

Balloon angioplasty is usually a first option to treat portal venous stenosis especially in children. "Leave nothing behind' is its main advantage, but relatively high incidence of elastic recoiling or restenosis is its limitation. Stent placement is usually considered as a second option owing to remaining foreign bodies in the portal venous system. However, long-term stent patency is relatively high (>90% for 5 years). Stent placement as well as variceal embolization or ligation via a mesenteric vein is an attractive method during liver transplantation, to ensure brisk portal venous inflow. Percutaneous thrombolysis or aspiration thrombectomy may help to manage intrahepatic portal vein thrombosis although open thrombectomy is the standard method to treat post-transplant portal vein thrombosis.

DAY 3: Saturday, June 18, 2016 (13:10-14:10) WEST TOWER Room C

KHBPS-JSHBPS Joint Symposium 1

Evidence Based Management for Hepatocellular Carcinoma

Chairs : Norihiro Kokudo (The Univ. of Tokyo)
Hee Jung Wang (Ajou Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Primary Liver Cancer Registry in Japan: How Has It Been Evolving?

Norihiro Kokudo

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Since 1969, The Liver Cancer Study Group of Japan (LCSGJ) has been conducting nationwide surveys on primary liver cancer patients every 2 or 3 years. After the 4th survey in 1978, patient data were collected using personal data sheet and the patients were followed-up until death or the most recent survey. The participating hospitals were LCSGJ member institutions numbering 400-600, and these surveys are estimated to cover 1/4 to 1/3 of all liver cancer patients treated in Japan. These surveys were based on the "General Rules for the Clinical and Pathological Study of Liver Cancer" proposed by LCSGJ and have been serving as valuable big clinical database for the clinical research.

According to the most recent report of the 19th follow-up survey (Kudo 2016 Hepatol Res 46:372-), a total of 20,850 primary liver cancer patients newly registered at 482 medical institutions over a period of 2 years (from 1 January 2006 to 31 December 2007). Of these, 94.7% had hepatocellular carcinoma (HCC) and 4.4% had intrahepatic cholangiocarcinoma (ICC). In addition, follow-up data were obtained regarding 34,752 patients who were registered in the previous survey.

Patient data collection following Act on the Protection of Personal Information (2003) has been a big issue and we have adopted electrical data collecting system since 2004. From 2016, our survey was integrated in National Clinical Database (http://www.ncd.or.jp), the national mega-database collecting more than one million surgical procedures conducted in Japan every year.

Random Sampling of Korea Central Cancer Registry for Hepatocellular Carcinoma

Young-Suk Lim

The Liver Cancer Registry Committee of KLCA,
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To provide evidence-based interventions in prevention, early diagnosis, treatment and palliative care, a national cancer control program is needed, and a population-based cancer registry is an essential element in national cancer control program in evaluating the current situation, setting objectives, and defining priorities.(Parkin 2008)

Populations are all people in a defined setting. Clinical populations include all patients with specific clinical characteristics such as hepatocellular carcinoma (HCC). A sample is a subset of people in the defined population. Researchers are interested in the characteristics of the defined population, but, for practical reasons, must estimate them by describing the characteristics of people in a sample. Thus, clinical research is ordinarily carried out on sample. We then make an inference, a reasoned judgment based on data, that the characteristics of the sample resemble those of the parent population. The extent to which a sample represents its population, and thus is a fair substitute for it, depends on how the sample was selected. Samples taken erroneously may misrepresent their parent population and so be misleading. Thus, random selection of the sample from the population is key essential first step to ensure that the sample can represent the population.

The Korean Liver Cancer Association (KLCA) has its own primary liver cancer registry (available at www.plcr.or.kr). This registry is based on voluntary reporting from the KLCA members, which is a web-based on-line registration registry since year 1990. KLCA voluntary registry has strength as it collects detailed information about the patients, tumors, and treatments. Nevertheless, as a voluntary reporting system, this registry is prone to serious selection bias.

The largest nationwide cancer registry in Korea is the Korea Central Cancer Registry (KCCR), executed by government-endorsed organization, which began cancer registry since 1980. The KCCR registry is statutory registry, and in Korea, patients diagnosed with cancer receive additional economic assistance by a medical reimbursement policy when registered at the KCCR; hence, almost all the incident cancers (> 95%) occurring in the population are reported in the registry.(Ahn 2007) KCCR registry has strength as it has case completeness defined as including all the incident cancers occurring in the population in the registry database, but has limitation as it lacks data completeness; it does not collect detailed information on clinical and tumor characteristics as well as treatment information.

Thus, in the year 2010, the KLCA HCC registry committee decided to conduct a random sample audit from KCCR registry, in order to collect unbiased information about the characteristics of the patients with HCC in Korea. Now, the KLCA has a large database of patients with HCC as follows:

- KLCA voluntary registry for patients diagnosed as HCC between 1990-2015
- KCCR random sample registry for 15% of patients diagnosed as HCC between 2003-2005 in Korea
- KCCR random sample registry for 13% of patients diagnosed as HCC between 2008-2010 in Korea
- KCCR random sample registry for 13% of patients diagnosed as HCC between 2010-2012 in Korea

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What and How to Build Up Solid Evidences for Surgical Treatment of Hepatocellular Carcinoma

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In order to provide the best treatment option to patients with hepatocellular carcinoma (HCC), it is essential to offer the patient based upon evidence based medicine. According to the level of evidence, a meta-analysis or systematic review of studies including randomized control trial studies have the strongest evidence. However randomized control trials in HCC is are not frequently done and even more for surgical treatment. HCC is more difficult to perform an RCT study compared to other cancers for several reasons. In order to have sufficient statistical power there must be sufficient cases per groups we want to compare. However, it is very difficult to group all types of HCC within few comparison groups. First, there are differences in the remnant liver is function –cirrhotic livers are different from chronic hepatitis or normal liver and there is still a wide range of differences of liver function within the same that should be taken into account when evaluating the outcome. Secondly, even though the tumor size may be the same, the different location of the tumor requires over 10 different types of operations from right extended hepatectomy to caudate lobectomy and wedge resection, which are very different from each other when looking from the surgical prospective. And finally to matters even more complex, the remnant liver volume should also be taken into consideration. A right hepatectomy for same liver function in a patient with an expected remnant liver volume of 25% is not the same as a patient with 40%. Therefore, it will most likely be very difficult to have a well powered RCT for HCC and the outcome obtained from one specific study for a specific operation or HCC will be difficult to be extrapolated for HCC requiring other types of operations located in different segments. Also some surgical procedures are not fit for a RCT.[1]

Here are some methods that may be used in the field of treatment options for HCC.

1.Registry

Registry is probably one of the best way to get high level of evidence in HCC. A registry must include not only selective patients from a center but all patients expecting to undergo surgical treatment. The patient should be registered not at time of operation but when the surgical decision is decided to have a proper intention to treat analysis. Furthermore, once a proper registry is formed, a randomized study within the registry may be done to improve the level of evidence.

2. Prospective data collection

Unlike the registry, this method is best used for a specific type of disease, such as portal vein tumor thrombosis. Compared to the registry, there usually requires much more variables during the data collection in order to properly evaluate the specific type of disease. A multicenter data collection is often necessary for speedy acquisition of the data but this should be weighed against the logistical complexity that is often necessary to get more centers involved. It is very important to not have loss of data especially when performing a multicenter study. There are currently many different internet based programs to support this.

3. Innovative surgical procedures[2]

It is important to have proper evaluation and acquire evidence in the surgical arena where new innovative surgical procedures are adapted. However, requiring high level of evidence for all new different types of surgical treatment will result to delayed adoption of new surgical treatment and is not beneficial. Nevertheless, it is also important, especially for the safety of the patient, to have a proper structured approach to new innovations such as the IDEAL model. The IDEAL model consists of Innovation, Development, Early dispersion and exploration, Assessment, and Long-term study.

- **Innovation stage**
  The primary aim of this stage is safety and proof of concept.
- **Development stage**
  Regulation and evidence from high-quality, well-designed studies such as the development of protocols and ethical approval is necessary.
- **Early dispersion and exploration stage**
  Mentoring and learning assessment are important, as is the collection of data for all patients. Preparation for a major large randomised trial should be done at this stage.
- **Assessment**
  By this stage the procedures are sufficiently well developed and effectiveness of the new surgical procedure should be tested against the current standard practice.
- **Long-term study**
  A registry should be established to monitor outcomes that are rare. Studies of outcome between different subgroups may be done.

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DAY 3: Saturday, June 18, 2016 (14:10-15:30) WEST TOWER Room C

KHBPS-JSHBPS Joint Symposium 2

Incorporating Recent Technologies in Liver Surgery

Chairs : Atsushi Sugioka (Fujita Health Univ.)
Dong-Sup Yoon (Yonsei Univ.)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Laparoscopic and Robotic Liver Resection Using Advanced 3D Liver Simulation Software

Atsushi Sugioka, Yutaro Kato, Yoshinao Tanahashi, Tadashi Kagawa, Masayuki Kojima, Sanae Nakajima, Syo-ichiro Tsuji, Ichiro Uyama

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Background: Minimally invasive liver resection including laparoscopic and robotic liver resection is a rapidly developing field with the greatest potential. However, the spatial disorientation is one of the biggest issues that would increase the risk of dangerous bleeding and bile leakage. To overcome this issue, it is of crucial importance to standardize anatomical liver resection with extrahepatic Glissonean pedicle-first approach and to use advanced 3D liver simulation software that can visualize the Glissonean system.

Methods: We proposed a novel concept of liver anatomy based on Laennec's capsule that can standardize the extrahepatic Glissonean pedicle approach. Whereas Synapse 3D® is the first simulation software to use face recognition technology for clinical 3D simulation and visualization of the Glissonean system are available since version 4.4.

Results: Owing to the novel concept of liver anatomy, anatomical liver resection with extrahepatic Glissonean pedicle-first approach was standardized and target area was well recognized prior to parenchymal dissection with minimal bleeding and bile leakage from the resecting plane. Preoperative 3D simulation and intraoperative navigation contributed to perform systematic anatomical liver resection without spatial disorientation even for the cases with anatomical abnormalities such as right-sided ligamentum teres.

Conclusion: Minimally invasive liver resection including laparoscopic and robotic resection became safe and curable procedures with the novel concept of liver anatomy and advanced 3D liver simulation.

Laparoscopic Liver Resection Using 3D Camera System

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Background and aims: Demand for minimal invasive surgery in case of liver tumor and iver donor in living donor liver transplantation (LDLT) is increasing because of several advantages of MIS including cosmetic outcomes which may influence their quality of life after donation. And three-dimensional vision using 3D laparoscopy appears to greatly enhance laparoscopic proficiency even in resection of segment 7 and 8 which is not accessible by 2D rigid scope.

Video contents: 3D laparoscopic hepatectomy shows better depth perception that cannot be achieved with traditional 2D systems, without any complaints about visual strains. This depth perception is important for accurate and swift dissection which is helpful in liver mobilization and parenchymal dissection. I will introduce our S7 tumorectomy and S8 tumorectomy which is relatively difficult considering location. Three-dimensional vision could reduce some intraoperative incidents particularly during parenchyma transection and give excellent hand eye coordination which is helpful in liver mobilization and resecting liver by Cavitron Ultasonic Surgical Aspirator (CUSA).

I will also introduce how our 3D laparoscopic heptectomy goes on showing from outside of the operation field. Three-dimensional vision could reduce some intraoperative incidents particularly during parenchyma transection and give excellent hand eye coordination which is helpful in resecting liver by Cavitron Ultasonic Surgical Aspirator (CUSA). Eventually 3D laparoscopy for donor hepatectomy allows better cosmetic outcomes.

Application of Indocyanine Green Fluorescence Imaging in Liver Resection

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Background: Fluorescence imaging has been recently used for an intraoperative real-time navigation worldwide. The aim of this report is to demonstrate liver resection that guided by fluorescence imaging using indocyanine green (ICG) as a fluorescence source.

Method: Three fluorescence imaging systems (PDE-neo, Hamamatsu Photonics; Olympus Medical Systems; PINPOINT, Novadaq) were used. ICG (Diagnogreen; Daiichi Sankyo, Tokyo, Japan) was administered as follows. *Liver cancer identification:* intravenous ICG injection at a dose of 0.5 mg/kg as a routine liver function test within 2 weeks before surgery. *Biliary anatomy visualization:* intravenous ICG injection (1 mL) or intrabiliary ICG injection (0.025 mg/mL) after intubation in the operating room. *Identification of regions flown by portal vein:* ICG injection (0.25 mg = 0.1 mL) to tumor-bearing portal veins after diluting it in 5 mL of indigo-carmine solution (20 mg, Daiichi Sankyo).

Results: *Liver cancer identification:* hepatocellular carcinoma can be identified as fluorescence due to impaired ICG excretion function in cancerous tissue compared to non-cancerous tissues. *Biliary anatomy visualization:* during surgery, the common bile duct was visualized after intrabiliary ICG injection. *Identification of regions flown by portal vein:* a tumor-bearing hepatic segment was visualized by injecting ICG with indigo-carmine under intraoperative ultrasonographic guidance. *ICG fluorescence-guided anatomic liver resection:* Portal vein branches feeding the cancer-bearing hepatic segments were visualized longitudinally and punctured with a 22G needle under IOUS guidance, followed by injection of ICG (0.25 mg 1/4 0.1 mL ICG) diluted in 5 mL of indigo-carmine solution (20 mg, Daiichi Sankyo).

Conclusion: Fluorescence imaging navigation facilitates identification of liver cancer, the bile duct, and hepatic segment and is expected to enhance the safety and efficacy during liver surgery.

Liver Resection Using Robotic System

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

The robotic system was first introduced in Korea in 2005 and then a total of 58 da Vinci systems have been installed in Korea, including 23 S systems, 22 Si systems and 13 Xi systems. The first robotic liver resection was cholecystectomy, which was performed by prof Lee in July 2005. The first robotic liver resection was performed in 2007 in Korea. The patient was 62-year-old female and had 2.4 cm sized hepatocellular carcinoma (HCC) in the left lateral section. She received robotic left lateral sectionectomy, which was published in 2008. All three patients who received left lateral sectionectomy showed good perioperative outcomes. It was the first report in Korea and a leading article about robotic liver resection in the world.

From Dec 2008 to May 2016, 69 patients underwent robotic liver resection using the da Vinci Surgical System® (Intuitive Surgical, Sunnyvale, CA) in Yonsei University Health System, Seoul, Korea. There were 53 malignant tumors (36 HCCs, 5 cholangiocellullar carcinomas, and 12 liver metastases from gastroinstestinal tract), 7 intrahepatic stones, 2 mucinous cystic neoplasms and 5 benign tumors. From the caudate lobe (S1) to segment 8, almost all types of liver resection have been performed, including 54 major hepatectomy. The median operation times of major and minor hepatectomy were 518 minutes and 360 minutes, respectively. Operative time seems to a littler longer in our series. When operative time was analyzed in 19 consecutive patients who received left hepatectomy alone, it became stabilized around 5 hours after the 10th case. The median estimated blood loss of major and minor hepatectomy was 200 ml and 100 ml, respectively. Six patients (8.7%) received perioperative transfusion. There were six conversions to open surgery (9.1%). The overall complication rate was 43.5%, but grade III complications occurred in only seven patients (10.6%). The median length of stay in the hospital was 8 days (range 5 - 46).

Our experience on robotic liver resection clearly demonstrates the feasibility and safety of all types of anatomic liver resections, recently even in more complex surgery such as ALPPS procedure and living donor right hepatectomy. However, because this experience is restricted to few centers, the feasibility and safety of robotic liver resection should be further demonstrated in larger and multi-intuitional studies.

DAY 3: Saturday, June 18, 2016 (08:30-09:50) EAST TOWER Room AB

Symposium 3

Nonalcoholic Fatty Liver Disease (NAFLD)

Chairs : Joung-Il Lee (Kyung Hee Univ.)
Seung Kew Yoon (The Catholic Univ. of Korea)

The Liver Week 2016

June 16-18, 2016 | Grand Hyatt Incheon, Korea

Lipid Droplet as a Potential Target for Nonalcoholic Fatty Liver Disease

Douglas G. Mashek

Department of Biochemistry, Molecular Biology and Biophysics and Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, University of Minnesota, Minneapolis, MN, USA

Non-alcoholic fatty liver disease (NAFLD) is defined by the presence of lipid droplets (LDs). Long thought to be inert energy storage depots, LDs are increasingly recognized as dynamic organelles that play key roles in linking changes in lipid metabolism and energy status to cell signaling and function. Despite their important roles, we are just beginning to identify proteins that reside on LDs and their biological functions. To date, the few LD proteins that have been characterized to any substantial degree affect a wide range of processes including energy metabolism, inflammation and NAFLD development and progression. Moreover, the expression level or mutations in specific LD proteins, such as PNPLA3, are known to robustly increase NAFLD risk. This presentation will overview our current understanding of hepatic LD proteins that may contribute to NAFLD etiology and their potential as therapeutic targets.

Noninvasive Diagnostic Method of Nonalcoholic Steatohepatitis

Eiji Miyoshi

Osaka University Graduate School of Medicine, Japan

Nonalcoholic fatty liver disease (NAFLD) is a growing medical problem and thus discriminating nonalcoholic steatohepatitis (NASH) from NAFLD is of great clinical significance. For NASH diagnosis, liver biopsy-proven histological examination is the current gold standard, and noninvasive and reliable biomarkers are greatly needed. Recently, we found two glycobiomarkers, fucosylated haptoglobin (Fuc-Hpt) and Mac-2 binding protein (Mac2bp), are useful independently for NASH diagnosis. Serum Fuc-Hpt is suitable for the prediction of ballooning hepatocytes and serum Mac2bp is suitable for the prediction of liver fibrosis severity. Combination of these 2 glycobiomarkers could make a noninvasive diagnosis of NASH in a large cohort of validation study. Using receiver-operating characteristic (ROC) analyses, area under the ROC curve (AUROC), sensitivity, and specificity of these 2 glycobiomarkers combination was 0.844, with 71.4% and 82.3%, respectively. In addition, we investigated the significance of our developed NASH diagnosis model in ultrasound-diagnosed NAFLD subjects who received medical health check-ups. Our model also could predict NAFLD disease severity in this larger population. Both Mac2-Bp and Hpt are target glycoproteins for fucosylation. Increases in serum fucosylated proteins are associated with hepatic inflammation as well as disrupt of membrane traffic in hepatocytes. In conclusion, the combination of serum Fuc-Hpt and Mac2bp can distinguish NASH from NAFLD patients. Our noninvasive model using two serum glycobiomarkers contributes to a novel NASH diagnostic methodology that could replace liver biopsy.

References

1. Nakagawa T, Miyoshi E *et al*, Journal of Proteome Res 11(5), 2012.
2. Kamada Y and Miyoshi E *et al*, Proteomics CA 7(9-10), 2013
3. Kamada Y and Miyoshi E *et al*, PLOS ONE 8(6), 2013
4. Kamada Y and Miyoshi E *et al*, Hepatology 62(5), 2015

Hepatocellular Carcinoma Development in Nonalcoholic Fatty Liver Disease

Luca Valenti

Universita degli Studi di Milano, Italy

Hepatocellular carcinoma (HCC) is the fourth cause of cancer related mortality, and its incidence is rapidly increasing. Viral hepatitis, alcohol abuse, and exposure to hepatotoxins are major risk factors. Nonalcoholic fatty liver disease (NAFLD) associated with obesity, insulin resistance, and type 2 diabetes, is an increasingly recognized trigger of HCC, especially in developed countries. Indeed, NAFLD may already represent the first cause of liver disease underlying HCC development in the UK and USA.
However, only a minority of NAFLD patients progresses to HCC. Older age, the severity of insulin resistance and in particular the presence of type 2 diabetes, moderate alcohol intake, and iron overload have been reported to predispose to HCC in patients with NAFLD. Remarkably, progressive NAFLD is a highly prevalent and mostly under-diagnosed condition, and it is frequently associated with several metabolic comorbidities. Furthermore, HCC have been reported to develop in non-cirrhotic livers in a much higher proportion of cases in NAFLD patients than in other etiologies. These factors render the implementation of current surveillance strategies very difficult for early diagnosis and curative treatment of NAFLD-HCC, leading to a diagnosis at advance stage a to a dismal prognosis in patients, with a reduced survival compared to that of patients affected by other liver diseases.
Inherited factors have also been implicated to explain the different individual susceptibility to develop HCC, and their role seems magnified in NAFLD, where only a minority of affected subjects progresses to cancer. In particular, the common I148M variant of the PNPLA3 gene influencing hepatic lipid metabolism increases HCC risk independently of its effect on the progression of liver fibrosis. However, common polymorphism in TM6SF2 and MBOAT7, and in familial cases mutations in APOB and TERT may also play a role.
A deeper understanding of the mechanisms mediating hepatic carcinogenesis during insulin resistance - NAFLD, and the identification of its genetic determinants will hopefully provide new diagnostic biomarkers to help stratifying disease risk and optimize surveillance and highlight novel therapeutic targets.

Molecular Targets for Nonalcoholic Steatohepatitis Therapeutics

Yong Kyun Cho

Department of Internal Medicine, Kangbuk Samsung Hospital,
Sungkyunkwan University School of Medicine, Seoul, Korea

The prevalence of NAFLD (Nonalcoholic fatty liver disease) is continuously growing worldwide and becoming pandemic disease in concert with ongoing epidemics of obesity, diabetes, and metabolic syndrome. Especially, NASH (Nonalcoholic steatohepatitis) has a potential to progress to cirrhosis or hepatocellular carcinoma and increased risk of liver related morbidity and mortality. Current treatment of NASH relies on lifestyle interventions such as behavioral, dietary, exercise changes, but there is no pharmacologic treatment approved as yet. So, we need to develop newer and effective anti-NASH drugs. Over the last years, accumulated understandings of the mechanism in NASH progression found out new therapeutic potential targets. Numerous newer drugs development program for NASH are ongoing and still in early clinical phase. Potential therapeutic targets including modulation of nuclear transcription factors, targeting lipotoxicity, oxidative stress, energy homeostasis, cellular metabolism, and resolution of hepatic inflammation and fibrosis. However, ongoing studies assessing novel drugs for NASH are yet far from clinical use in real practice. Here we review the major mechanisms leading to progression of NASH and identify the most promising molecular targets for the treatment of this condition. Strategies selection of optimal therapeutic target molecule and development of newer drugs may enable us to indivisualized and tailored treatment in NASH patients in the near future.

AUTHOR INDEX

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References) 1. DAKLINZA Product Information **2.** SUNVEPRA Product Information **3.** Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010;139:1593-1601. **4.** EASL Recommendations on Treatment of Hepatitis C 2015Clinical Practice Guidelines: Management of hepatitis C virus infection *J Hepatol* 2015;63:199-236

Daklinza Tablet 60mg (daclatasvir dihydrochloride) **[Active Ingredient]** Each 315mg tablet contains 66mg of daclatasvir dihydrochlorid·····In house specification **[Product Description]** Light green, biconvex, pentagonal film coated tablet **[Indications]** The treatment of chronic hepatitis C virus (HCV) of genotype 1b infection in adults with compensated liver disease (including cirrhosis) in combination with other medicine. **[Dosage and Administration] 1. Recommended Dosage** The recommended dose of this drug for the treatment of chronic HCV genotype 1b infection is 60mg, taken orally, once daily with or without food, in combination with asunaprevir 100mg (twice daily) for 24 weeks. **2. Dose Modification and Temporary Interruption** Once treatment is started, dose modification of this drug is not recommended. Refer to the respective prescribing information for dose modification of other medicines in the regimen. Treatment interruption should be avoided; however, if treatment interruption of any agent in the regimen is necessary because of adverse reactions, this drug must not be given as monotherapy. Patients should be instructed that, if they miss a dose of this drug, the dose should be taken as soon as possible if remembered within 20 hours of the scheduled dose time. However, if the missed dose is remembered more than 20 hours after the scheduled dose, the dose should be skipped and the next dose taken at the appropriate time. **3. Discontinuation** Regularly monitor hepatitis C virus ribonucleic acid (HCV RNA) levels during treatment. Patients with an inadequate on-treatment virologic response during treatment are unlikely to achieve sustained virologic response (SVR) and may develop resistance-associated substitutions. Discontinue the entire HCV treatment regimen for patients experiencing confirmed virologic breakthrough (greater than 1 log10 IU/mL increase in HCV RNA from nadir or achieve undetectable RNA (< LLOQ), but then confirmed into having detectable RNA (≥LLOQ) during treatment). **[Warnings and Precautions] 1. Contraindications** 1) This drug is contraindicated in patients with previously demonstrated hypersensitivity to this drug or any component of the product. 2) Since this drug is used in combination with other agents, the contraindications applicable to those agents are applicable to the combination regimen. Refer to the respective prescribing information for a list of contraindications. 3) Pregnancy or in women of childbearing potential 4) This drug is contraindicated in combination with drugs that strongly induce CYP3A4 and, thus, may lead to lower exposure and loss of efficacy of this drug. 5) Since this drug contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine. ※For more detailed information of the product, refer to the full prescribing information.

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[c] Sustained virologic response (SVR) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment. Achieving SVR is considered a virologic cure.

[d] When studied in combination with RBV ± Peg-IFN

References 1. Ahn SH, et al. Korean patients with genotype 1 and 2 HCV infection achieved over 97% sustained virologic response following 12 weeks of ledipasvir/sofosbuvir or sofosbuvir plus ribavirin. Asia Pacific Association for the Study of the Liver. Istanbul, Turkey, 2015. Abstract no. 1977. **2.** Sovaldi Product Information. http://drug.mfds.go.kr **3.** WHO. Guidelines for the screening, care and treatment of persons with hepatitis infection. April 2014. Available at: http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/ **4.** European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2014. J Hepatol. 2014:61:373-95. **5.** AASLD and IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. Revised Date: February 24, 2016. Available at: http://www.hcvguidelines.org **6.** Available at http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-earnings. Accessed Nov. 2015.

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[제품명] 바라클정 0.5mg, 1mg(엔테카비르) **[성분 · 함량]** 바라클정 0.5mg : 이 약 1정(206mg) 중 엔테카비르(별규) 0.53mg(엔테카비르 무수물로서 0.5mg) 바라클정 1mg : 이 약 1정(412mg) 중 엔테카비르(별규) 1.06mg(엔테카비르 무수물로서 1mg) 청가제(타르색소) : 적색40호 알루미늄레이크, 황색5호 알루미늄레이크, 청색2호 알루미늄레이크 **[성상]** 바라클정 0.5mg : 홍색~회백색의 삼각형 모양의 필름코팅정 바라클정 1mg : 분홍색의 삼각형 필름코팅정 **[효능 · 효과]** 활동성 바이러스의 복제가 확인되고, 혈청 아미노전이효소(ALT 또는 AST)의 지속적 상승 또는 조직학적으로 활동성 질환이 확인된 성인(16세 이상)의 만성 B형 간염바이러스 감염의 치료 **[용법 · 용량]** • 이 약은 공복 시 (식사 2시간 후 또는 최소 2시간 전) 경구투여합니다. • 이 약은 1일 1회 엔테카비르로서 0.5mg 을 경구투여합니다. • 라미부딘 저항성 환자, 즉, 라미부딘 치료에도 불구하고 B형간염바이러스의 지속적 증식을 경험하였거나, 라미부딘저항성 변이가 있는 16세이상의 환자 : 1일1회 공복시 엔테카비어로서 1mg • 신부전환자 : 신부전 환자에서는 크레아티닌 청소율이 감소함에 따라 이 약의 경구 소실율은 감소합니다. 혈액투석이나 복막투석(CAPD)을 받고 있는 환자를 포함하여 크레아티닌 청소율이 50mL/min 미만인 환자에서는 다음과 같이 용량을 조절합니다.

크레아티닌 청소율(mL/min)	엔테카비어 용량	라미부딘 저항성 환자에서의 엔테카비어 용량
≥ 50	1일1회 0.5 mg	1일1회 1 mg
30 – <50	1일1회 0.25 mg [a] 또는 48시간마다 0.5 mg	1일1회 0.5 mg 또는 48시간마다 1 mg
10 – <30	1일1회 0.15 mg [a] 또는 72시간마다 0.5 mg	1일1회 0.3 mg a 또는 72시간마다 1 mg
<10, 혈액투석 b 또는 CAPD	1일1회 0.05 mg [a] 또는 7일마다 0.5 mg	1일1회 0.1 mg a 또는 7일마다 1 mg

a : 0.5mg보다 적은 용량은 시럽제 사용이 권장된다.
b : 혈액투석 일에 투여된다면, 혈액투석 과정 후에 이 약을 투여한다.
(신부전 환자에서의 약동학적 특성 : 상세정보 기타 : 신부전환자에 대한 투여 참조)

[사용상의 주의사항] 1. 경고 1) 뉴클레오시드 유사체 단독사용 또는 엔테카비르를 포함한 항레트로바이러스제와 병용했을때, 치명적인 경우를 포함하여, 유산증 및 지방증이 있는 중증 간종대가 보고되었습니다.이들 대부분은 여성에서 발생했습니다. 비만과 지속된 뉴클레오시드 사용이 위험인자들일수 있습니다. 간질환에 대한 알려진 위험인자 등을 가진 환자에게 뉴클레오시드 유사체를 투여할 때에는 각별한 주의가 요구됩니다. 하지만, 알려진 위험인자들을 가지고 있지 않은 환자에서도 보고된 사례가 있었습니다. 유산증이 보고되었으며, 중증 간대사기능장애, 다른 심각한 의학적 상태(medicalcondition) 또는 약물노출과 관련된 것이었습니다. 간대사기능장애를 가진 환자의 경우 유산증 위험성이 더 높습니다.이 약을 사용한 치료는 유산증이나 명백한 간독성(트랜스아미나제 수치의 상승없는 간종대와 지방증을 포함)을 나타내는 임상적 발견 또는 임상검사치가 나타나면 일시 중지되어야 합니다. 2) 이 약을 비롯한 B형간염 요법을 중단한 환자에서 B형간염의 중증 급성악화가 보고되었습니다. B형B형간염 요법을 중단한 환자에 대해서는 적어도 수 개월간 임상 및 임상검사상 간기능을 면밀하게 추적 관찰해야 합니다. 적절한 경우, B형B형간염 요법을 개시할수 있습니다. 3) 이 약은 효과적인 HIV(인체면역결핍바이러스)치료를 받고 있지 않는 HIV와 HBV에 함께 감염된 환자들을 대상으로 평가되지 않았습니다. HIV에 감염되었지만 아직 치료받지 않은 환자에게 만성 B형감염의 치료로 이 약이 사용된다면 HIV 뉴클레오시드 역전사효소 억제제에 대한 저항성을 나타낼 수 있음이 제한된 임상시험 경험에서 나타났습니다. 그러므로 고효능 항레트로바이러스 치료법(HAART)으로 함께 치료받고 있지 않은 HIV/HBV 동시 감염 환자에게는 이 약을 사용한 치료가 권장되지 않습니다. 이 약을 사용하기 전에 환자들은 HIV 항체 테스트가 필요합니다.
이 약은 HIV감염의 치료목적으로 연구되지 않았고 이러한 목적으로 권장되지 않습니다. 2. 다음 환자에는 투여하지 마십시오. 1) 이 약이나 이 약의 성분에 과민반응이 있는 환자2) 이 약은 유당수화물을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance,Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactosemalabsorption) 등의 유전적인 문제가 있는 환자 3. 다음 환자에는 신중히 투여하십시오. 1) 신부전 : 혈액투석 또는 복막투석(CAPD)을 받고 있는 환자를 포함하여 크레아티닌 청소율이 50 mL/min이하인 환자에서는 용량조절이 권장됩니다. 2) 간이식 수여자 : 싸이클로스포린이나 타크롤리무스와 같이 신장 기능에 영향을 줄 수 있는 약물을 투여 받고 있는 간이식수여자에서 이 약의 요법을 개시하기 전 및 치료 중에 신기능을 주의하여 평가해야 합니다. 3) 이 약은 황색5호(샛앨로우 FCF, Sunset Yellow FCF)를 함유하고 있으므로 이 성분에 과민하거나 알레르기 병력이 있는 환자에는 신중히 투여합니다. **※자세한 제품정보는 제품설명서를 참고해 주십시오**

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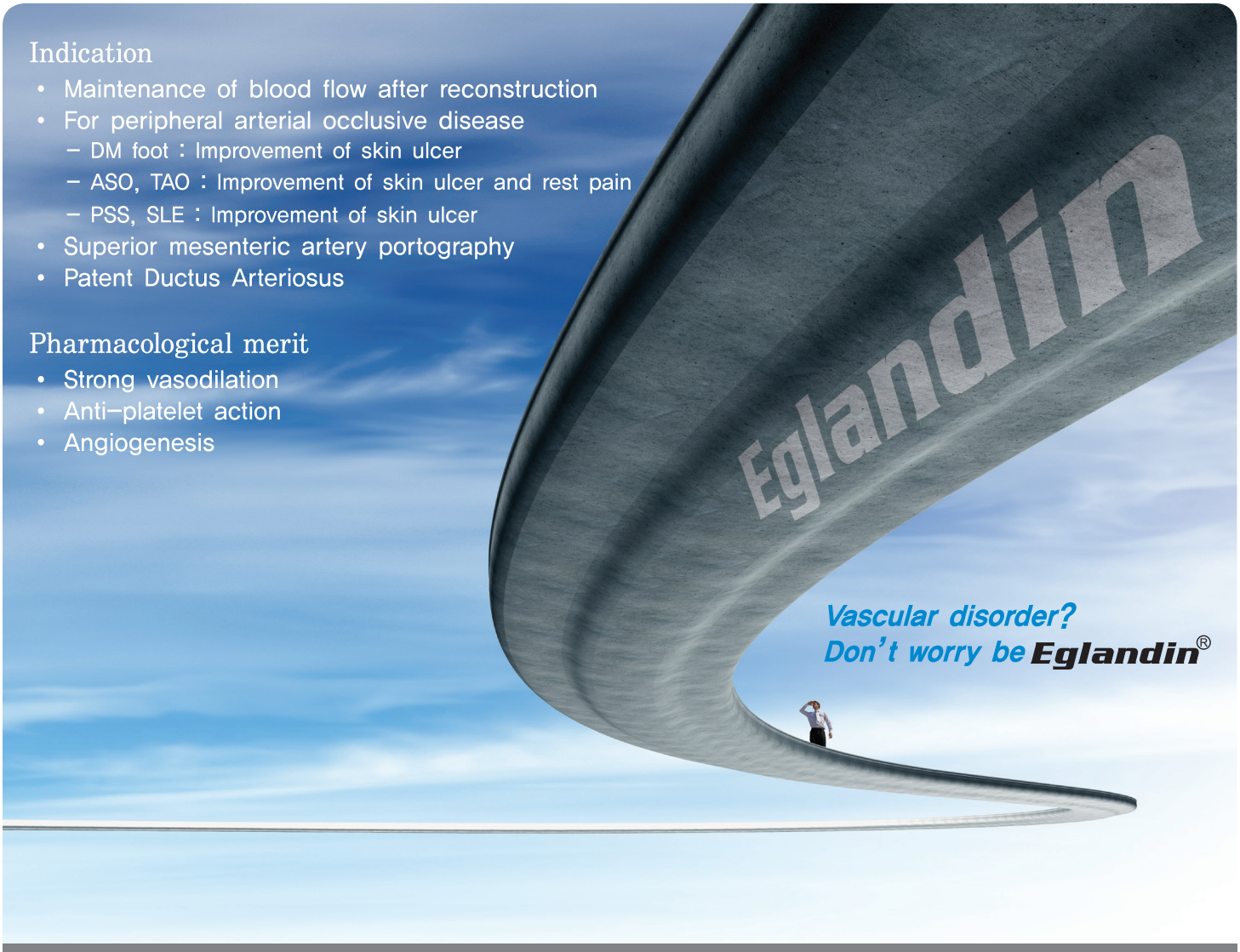
- Superior mesenteric artery portography
- Patent Ductus Arteriosus

Pharmacological merit

- Strong vasodilation
- Anti-platelet action
- Angiogenesis



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Pharmacological merit

- Strong vasodilation
- Anti-platelet action
- Angiogenesis

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*LRT=Locoregional therapies
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Indications 1) Hepatocellular carcinoma 2) Patients with advanced renal cell carcinoma who have failed prior cytokines therapy or are considered unsuitable for such therapy 3) Patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma that is refractory to radioactive iodine treatment
Dosage and Administration
- The recommended daily dose: 400mg (2 tablets) orally twice daily without food (at least 1 hour before or 2 hours after a meal)
- Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions. Temporary interruption or dose modification of NEXAVAR may be required for the management of adverse events.

*** For suggested dose modifications for dermatologic toxicities and further detailed dosage and administration information, please refer to the full NEXAVAR® local product information**
Warnings
Based on its mechanism of action and findings in animals, NEXAVAR may cause fetal harm when administered to a pregnant woman. Sorafenib caused embryo-fetal toxicities in animals at maternal exposures that were significantly lower than the human exposures at the recommended dose of 400 mg twice daily. There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. NEXAVAR should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. The patient should discontinue the drug during nursing.
Contraindication Patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR
Adverse Reactions
The data of adverse reactions related to NEXAVAR reflect exposure to NEXAVAR in 955 patients who participated in placebo controlled studies in hepatocellular carcinoma (N=297), advanced renal cell carcinoma (N=451), or differentiated thyroid carcinoma (N = 207). The most common adverse reactions, which were considered to be related to NEXAVAR are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash. Very common adverse reactions (≥10%) are infection, lymphopenia, loss of appetite, hypophosphatemia, haemorrhage, hypertension, diarrhea, nausea, vomiting, constipation, dry skin, rash, alopecia, hand-foot skin reaction, itchiness, red spots, pain, fatigue, fever, weight loss, increased lipase, increased amylase.
Ethical Drug
Imported and Marketed by Bayer Korea Ltd. Korea
The latest revision date: 11-Nov-2014
For further detailed information, please refer to the full NEXAVAR® local product information or Bayer Korea website, http://www.bayer.co.kr/

References: 1. Llovet JM, Ricci S, Mazzaferro V, et al; for the SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378-390. **2.** Cheng A-L, Kang Y-K, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10(1):25-34. **3.** Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53(3):1020-1022.

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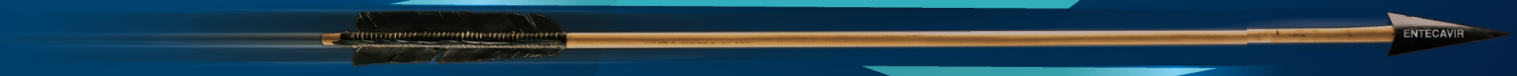

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뇌혈관·심장혈관·말초동맥질환

■ 효능 · 효과 : 1. 허혈뇌졸중, 심근경색 또는 말초동맥성질환이 있는 환자에서 죽상동맥경화성 증상의 개선 2. 급성관상동맥증후군[불안정성 협심증 또는 비Q파 심근경색 환자에 있어서, 약물치료 또는 관상중재시술(PCI)(stent 시술을 하거나 하지 않은 경우) 및 관상동맥회로우회술(CABG)을 받았거나 받을 환자를 포함]이 있는 성인 환자에서 죽상동맥경화성 증상(심혈관계 이상으로 인한 사망, 심근경색, 뇌졸중 또는 불응성 허혈)의 개선 3. 한 가지 이상의 혈관성 위험인자를 가지고 있고, 비타민 K 길항제(VKA) 투여가 적합하지 않으며, 출혈 위험이 낮은 심방세동 성인환자에서 뇌졸중을 포함한 죽상혈전증 및 혈전색전증의 위험성 감소 ■ 용법 · 용량 : 1. 허혈뇌졸중, 심근경색 또는 말초동맥성 질환이 있는 환자에는 클로피도그렐로서 1일 1회 75㎎을 경구투여한다. 2. 급성관상동맥증후군(불안정성 협심증 또는 비Q파 심근경색)이 있는 환자에는 이 약 투여개시일에 이 약으로서 1일 1회 300㎎을 부하용량(loading dose)으로 시작하고 이후에 1일 1회 75㎎을 유지 용량으로 경구투여한다. 이 때, 아스피린 75~325㎎을 1일 1회 이 약과 병용투여하여야 한다. 3. 심방세동 환자에는 이 약으로서 1일 1회 75㎎을 경구투여한다. 이 때 아스피린 75~100㎎을 1일 1회 이 약과 병용투여 하여야 한다.

*소비자상담전화 : 080-082-1234(수신자부담) www.samjinpharm.co.kr

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Functions of the liver cell mitochondria

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4. Activating immune cells in the liver to release cytokines (IL, TGF, TNF)

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- Variability in calcineurin inhibitor exposure can result in reduced renal function or graft life[1-3]
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- Prolonged-release ADVAGRAF has been engineered to deliver a lifetime of consistent, predictable control of tacrolimus exposure[5]

References: 1. Waiser J, Slowinski T, Brinker-Paschke A, et al. *Nephrol Dial Transplant.* 2002;17(7):1310-1317. **2.** Kahan BD, Welsh M, Urbauer DL, et al. *J Am Soc Nephrol.* 2000;11(6):1122-1131. **3.** Stoves J, Newstead CG. *Transplantation.* 2002;74(12):1794-1797. **4.** Borra LC, Roodnat JI, Kal JA, et al. *Nephrol Dial Transplant.* 2010;25(8):2757-2763. **5.** European Medicines Agency. European public assessment report (EPAR): Advagraf: scientific discussion.

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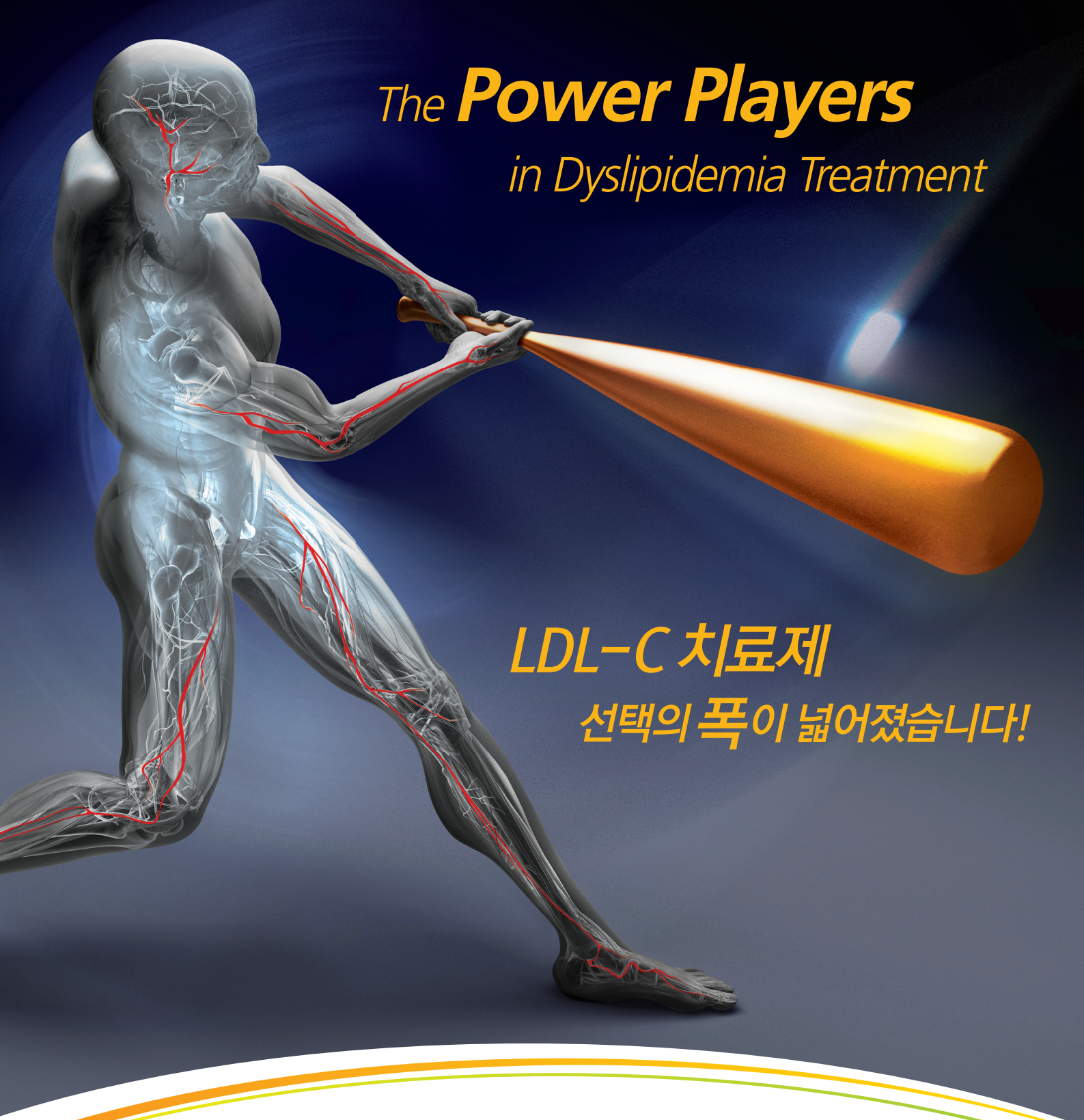

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(entecavir)

· 경제적 약가 · 생물학적 동등성 입증

【원료약품의 분량】 카비어정 : 엔테카비르 **【성 상】** 카비어정0.5mg : 백색-회백색의 삼각형 모양의 필름코팅정 / 카비어정 1mg : 분홍색의 삼각형 모양의 필름코팅정 **【효능 · 효과】** 활동성 바이러스의 복제가 확인되고, 혈청 아미노전이효소(ALT 또는 AST)의 지속적 상승 또는 조직학적으로 활동성 질환이 확인된 성인(16세 이상)의 만성 B형 간염바이러스 감염의 치료 **【용법 · 용량】** 공복 시 (식사 2시간 후 또는 최소 2시간 전) 경구투여한다. 자세한 사항은 첨부문서 참조. **【제품문의】** 소비자상담실 : 080-916-9000(수신자요금부담)

For healthcare professionals only

Hepsera™ Regained control, Sustained control

In LMV-resistant patients, combined ADV-LMV therapy attenuated the risk of genotypic resistance to ADV, preventing virologic and clinical break-through during a 3-year period.[1]

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References

1. Lampertico P, Vigano M, Manenti E, et al. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology. 2007;133(5):1445-51.

Safety Information

1. **Special warnings** 1) Higher doses must not be administered. 2) If treatment cessation is necessary, patients should be closely monitored for several months after stopping treatment as exacerbations of hepatitis have occurred after discontinuation of 10 mg adefovir dipivoxil. 3) Long-term treatment with adefovir dipivoxil may increase the risk of renal impairment. 4) Prior to initiating HEPSERA therapy, HIV antibody testing should be offered to all patients. 5) Treatment of hepatitis B by adefovir dipivoxil in an HIV co-infected patient should be reserved for patients whose HIV RNA is controlled(<400 copies/mL). 6) Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. 7) Other • 1 Patients should be advised that therapy with adefovir dipivoxil has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore appropriate precautions should still be taken. • 2 HEPSERA should be administered with care to patients with known carnitine deficiency (congenital). • 3 Adefovir dipivoxil should not be administered concurrently with tenofovir disoproxil fumarate or tenofovir disoproxil fumarate-containing products
2. **Contrainications** 1) Hypersensitivity to the active substance or to any of the excipients. 2) Hepsera contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, theLapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.
3. **Precautions**: the contributory role of HEPSERA to these changes in renal function is difficult to assess.
4. **Adverse reactions** 1) Adverse reactions reported in ≥3% of All HEPSERA-Treated Patients in two studies, where 522 patients with chronic hepatitis B and compensated liver disease received double-blind treatment for 48 weeks include following: asthenia, headache, abdominal pain.

Abbreviated PI version 02

Prescription only | Imported product

[Abbreviated Prescribing information] Hepsera 10 mg tablets ■ Qualitative and quantitative composition Each tablet contains 10 mg adefovir dipivoxil. ■ Therapeutic indications HEPSERA is indicated for the treatment of chronic hepatitis B in patients 12 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. This indication is based on histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function, and with clinical evidence of lamivudine-resistant hepatitis B virus with either compensated or decompensated liver function. ■ Dosage and administration Adults: The recommended dose of Hepsera is 10 mg once daily. Renal impairment: Adefovir is eliminated by renal excretion and adjustments of the dosing interval are required in patients with a creatinine clearance < 50 ml/min or on dialysis. ■ Warnings and precautions for use 1. Special warnings 1) Higher doses must not be administered. 2) If treatment cessation is necessary, patients should be closely monitored for several months after stopping treatment as exacerbations of hepatitis have occurred after discontinuation of 10 mg adefovir dipivoxil. 3) Long-term treatment with adefovir dipivoxil may increase the risk of renal impairment. It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with adefovir dipivoxil. In patients at risk for renal impairment, consideration should be given to more frequent monitoring of renal function. In patients who develop renal insufficiency and have advanced liver disease or cirrhosis, dosing interval adjustment of adefovir or switch to an alternative therapy for hepatitis B infection should be considered. 4) Prior to initiating HEPSERA therapy, HIV antibody testing should be offered to all patients. Treatment with anti-hepatitis B therapies, such as HEPSERA, that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance. 5) Treatment with 10 mg adefovir dipivoxil has not been shown to be effective against HIV replication. Treatment of hepatitis B by adefovir dipivoxil in an HIV co-infected patient should be reserved for patients whose HIV RNA is controlled(<400 copies/mL). 6) Occurrences of lactic acidosis (in the absence of hypoxaemia), sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues. As adefovir is structurally related to nucleoside analogues, this risk cannot be excluded. 7) Other • 1Patients should be advised that therapy with adefovir dipivoxil has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore appropriate precautions should still be taken. • 2 HEPSERA should be administered with care to patients with known carnitine deficiency (congenital). • 3Adefovir dipivoxil should not be administered concurrently with tenofovir disoproxil fumarate or tenofovir disoproxil fumarate-containing products including emtricitabine/tenofovir disoproxil fumarate combination tablet, efavirenz/emtricitabine/tenofovir disoproxil fumarate combination tablet. 2. Contrainications 1) Hypersensitivity to the active substance or to any of the excipients. 2) Hepsera contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product. 3. Precautions: Changes in renal function occurred in pre-and post-liver transplantation patients with risk factors for renal dysfunction, including concomitant use of cyclosporine and tacrolimus, renal insufficiency at baseline, hypertension, diabetes, and on-study transplantation. Therefore, the contributory role of HEPSERA to these changes in renal function is difficult to assess. 4. Adverse reactions 1) Adverse reactions reported in ≥3% of All HEPSERA-Treated Patients in two studies, where 522 patients with chronic hepatitis B and compensated liver disease received double-blind treatment for 48 weeks include following: asthenia, headache, abdominal pain. Laboratory abnormalities reported in ≥1% include following: ALT, hematuria, AST. Laboratory abnormalities observed in these studies occurred with similar frequency in the 10 mg HEPSERA and placebo-treated groups with the exception of hepatic transaminase elevations which occurred more frequently in the placebo-treated group. Increased creatinine was identified as an adverse reaction with extended open-label treatment in two studies. 5. Use in pregnancy 1) There are no adequate and well-controlled studies of HEPSERA in pregnant women. HEPSERA should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits. 2) There are no studies in pregnant women and no data on the effect of HEPSERA on transmission of HBV from mother to infant. Therefore, appropriate infant immunizations should be used to prevent neonatal acquisition of hepatitis B virus. 3) It is recommended that mothers being treated with adefovir dipivoxil do not breast-feed their infants. 4) No human data on the effect of adefovir dipivoxil on fertility are available. The use of adefovir dipivoxil must be accompanied by the use of effective contraception. 6. Children and adolescents (<18 years): The safety and efficacy of HEPSERA in patients under the age of 18 years have not been established. ■ Last date of revision 13/11/2015 ■ Detailed information on this medicinal product is available on the website of GlaxoSmithKline Korea www.gsk-korea.co.kr. Adverse events for GSK products should be reported to GlaxoSmithKline Korea on 080-901-4100 or kr-medical.drug-safety@gsk.com.

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