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
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 HPB Surgery (KHBPS), the Korean Liver Cancer Association (KLCA) and the Korean Liver Transplantation Society (KLTTS), 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 Joo
Vice President
The Liver Week 2016
<table>
<thead>
<tr>
<th>Role</th>
<th>Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congress Chairman</td>
<td>Yung Sang Lee</td>
</tr>
<tr>
<td>Congress President</td>
<td>Kwan Soo Byun</td>
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<tr>
<td>Congress Vice President</td>
<td>Kyung Suk Suh, Soon Ho Um, Jae Won Joh</td>
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<tr>
<td>Secretary General</td>
<td>Han Chu Lee, Nam-Joon Yi, Hyung Joon Yim, Gyu-Seong Choi</td>
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<tr>
<td>Scientific Committee Chair</td>
<td>Jong Eun Yeon</td>
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<tr>
<td>Scientific Committee Vice Chair</td>
<td>Jin Young Jang, Do Young Kim, Chong Woo Chu</td>
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<tr>
<td>Treasurer</td>
<td>Ji Hoon Kim</td>
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<tr>
<td>Organizing Committee Members</td>
<td>Kuk Hwan Kwon, Kang Mo Kim, Kyung Sik Kim, Myoung Soo Kim</td>
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<td>Sang Geol Kim, Yoon Jun Kim, In Hee Kim, Hyung Joon Kim</td>
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<td>Deok-Bog Moon, Sang-Jae Park, Il Young Park, Yong-Han Paik</td>
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<td>Yeon Seok Seo, Hee Jung Wang, Hee Chul Yu, Myunghee Yoon</td>
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<td>Kwang-Woong Lee, Jung Il Lee, Hyeon Kook Lee, Young-Suk Lim</td>
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<td>Byoung Kuk Jang, Jae Young Jang, Dae Won Jun, Ha Jong Chun</td>
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<td>Gi Hong Choi, Donglak Choi, Moon Seok Choi, Won Hyeok Choe</td>
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<td>In Seok Choi, Jong Young Choi, Jin Seok Heo, Shin Hwang</td>
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<td>Time</td>
<td>ROOM AB</td>
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<tr>
<td>08:00</td>
<td>* Postgraduate Course:</td>
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<td></td>
<td>Recent Update of Chronic Liver Disease (CLD) Treatment</td>
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<tr>
<td>09:00</td>
<td>PG1. Management of Viral CLD, LC, and HCC™</td>
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<td>(08:30-10:10)</td>
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<td>10:00</td>
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<td>11:00</td>
<td>PG2. Management of Non-viral CLD™</td>
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<td>13:00</td>
<td>Luncheon Symposium 1</td>
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<td>(by Yuhan)</td>
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<tr>
<td>14:00</td>
<td>PG3. Diagnosis and Management of Metabolic Complications in CLD™</td>
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<td>15:00</td>
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<tr>
<td>16:00</td>
<td>PG4. Organ Dysfunction in CLD™</td>
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<tr>
<td>08:30-10:10</td>
<td>PG1: Management of Viral Chronic Liver Disease, Liver Cirrhosis, and Hepatocellular Carcinoma</td>
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<tr>
<td>08:30-08:55</td>
<td>Chronic Hepatitis C Treatment: KASL Clinical Guidelines</td>
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<td>08:55-09:20</td>
<td>Hepatitis B Virus Treatment</td>
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<td>09:20-09:45</td>
<td>Management of Advanced Hepatocellular Carcinoma</td>
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<td>09:45-10:10</td>
<td>Treatment of Portal Hypertension Related Complications</td>
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<td>10:10-10:30</td>
<td>Coffee Break</td>
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<tr>
<td>10:30-10:55</td>
<td>Management of Non-viral Chronic Liver Disease</td>
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<tr>
<td>10:55-11:20</td>
<td>Treatment for Non-alcoholic Fatty Liver Disease</td>
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<td>11:20-11:45</td>
<td>Treatment of Autoimmune Hepatitis and Primary Biliary Cirrhosis</td>
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<td>11:45-12:10</td>
<td>Vaccinations for Adults with Chronic Liver Disease</td>
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<td>12:10-13:10</td>
<td>Luncheon Symposium 1 [by Yuhan]</td>
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<tr>
<td>13:10-14:50</td>
<td>PG3: Diagnosis and Management of Metabolic Complications in Chronic Liver Disease</td>
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<td>13:10-13:35</td>
<td>Diagnosis and Management of Metabolic Syndrome and Obesity in Chronic Liver Disease</td>
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<td>Diagnosis and Management of Osteoporosis and Vitamin D Deficiency in Chronic Liver Disease</td>
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<td>Diagnosis and Management of Dyslipidemia in Chronic Liver Disease</td>
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<td>14:25-14:50</td>
<td>Diagnosis and Management of Diabetes Mellitus in Chronic Liver Disease Focusing on Fatty Liver</td>
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<td>PG4: Organ Dysfunction in Chronic Liver Disease</td>
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<td>15:10-15:35</td>
<td>Diagnosis and Management of Heart Failure in Chronic Liver Disease</td>
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<td>15:35-16:00</td>
<td>Diagnosis and Management of Thyroid and Adrenal Dysfunction in Chronic Liver Disease</td>
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<td>Diagnosis and Management of Renal Dysfunction in Chronic Liver Disease</td>
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<td>16:25-16:50</td>
<td>Sepsis in Cirrhosis - Perspective by New Sepsis Guidelines 2016</td>
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</table>
| 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.)  
Yong Song Gho, POSTECH |
| 08:30-09:10| Exosome                                                                |
| 09:10-09:30| Exosome and Liver Disease                                               |
| 09:30-10:10| Role of Autophagy in Liver Injury                                       |
| 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.)  
Seong-Jun Kim, Korea Research Institute of Chemical Technology |
| 10:30-11:10| Autophagy in Chronic Viral Hepatitis                                   |
| 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                                          |
| 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                                    |
| 13:50-14:20| RCT: From an Idea into a Practice                                      |
| 14:20-14:50| Cohort Study: From an Idea into a Practice                             |
| 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)  
Kengo Yoshimitsu, Fukuoka Univ.  
Yoon Jun Kim, Seoul National Univ. |
| 15:10-15:40| From an Idea into a New Device: MR Elastography                        |
| 15:40-16:10| From an Idea into a New Drug: Olitipraz                                |
| 16:10-16:50| How to Prove Cost-effectiveness in My Research                         |

Jeonghwaon Ahn, Ewha Womans Univ.
# Program at a Glance

## DAY 2  Friday, June 17, 2016

<table>
<thead>
<tr>
<th>ROOM AB</th>
<th>ROOM C</th>
<th>ROOM D</th>
<th>ROOM A</th>
<th>ROOM B</th>
<th>ROOM C</th>
<th>ROOM D</th>
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<td>08:00</td>
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<td>09:00</td>
<td>KLTSC Symposium 1&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>12:00</td>
<td>Luncheon Symposium 3</td>
<td>by BMS</td>
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<td>Press Conference</td>
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<td>13:00</td>
<td>Luncheon Symposium 4</td>
<td>by Dong-A ST</td>
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<td>Lunch Break</td>
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<td>14:00</td>
<td>Special Lecture 1</td>
<td>(13:10-13:40)</td>
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<td>15:30</td>
<td>Coffee Break &amp; Poster Oral Presentation</td>
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<td>16:30</td>
<td>Special Interest Group Symposium 1</td>
<td>NAFLD</td>
<td>(16:30-18:10)</td>
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<td>18:30</td>
<td>Faculty Dinner</td>
<td>(18:00-20:00)</td>
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**The Korean Association for the Study of the Liver (KASL)**
**The Korean Association of Hepatobiliary Surgery (KHBPS)**
**The Korean Liver Cancer Association (KCLA)**

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**Laboratory Location**

**WEST TOWER**

**EAST TOWER**

**K: Session in Korean**
### WEST TOWER

**Room AB [B1]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>08:30-09:50</td>
<td>Symposium 1: Hepatitis C Virus</td>
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<tr>
<td>08:30-08:50</td>
<td>Appropriate Application of Direct Acting Antivirals</td>
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<td>08:50-09:10</td>
<td>Current Strategy for Chronic Hepatitis C Treatment in Korea</td>
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<td>09:10-09:30</td>
<td>Towards IFN-free Treatment: DCV+ASV for Genotype 1</td>
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<td>09:30-09:50</td>
<td>Management of Direct Antiviral Agent Failures</td>
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<td>09:50-10:10</td>
<td>Coffee Break</td>
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<tr>
<td>10:10-12:10</td>
<td>Plenary Session 1</td>
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<td>12:10-13:10</td>
<td>Luncheon Symposium 3 [by BMS]</td>
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<tr>
<td>13:10-13:40</td>
<td>Special Lecture 1</td>
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<tr>
<td>13:50-15:30</td>
<td>Clinical Hepatology Update</td>
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<td>13:50-14:10</td>
<td>Clinical Hepatology Update: Changes of DDLT Waiting Priority in Korea</td>
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<td>14:10-14:30</td>
<td>Diagnosis of Sub-centimeter Sized Hepatocellular Carcinoma</td>
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<td>14:30-14:50</td>
<td>Nonalcoholic Steatohepatitis: Diagnosis and Treatment Update</td>
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<td>14:50-15:10</td>
<td>Hepatitis C Virus: One Pill Is Enough for All Genotype</td>
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<td>15:10-15:30</td>
<td>Hepatitis B Virus: Changing Antiviral Treatment Strategies: Low Viral Load in Liver Cirrhosis with Hepatitis B Virus</td>
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<td>15:30-16:30</td>
<td>Coffee Break &amp; Poster Oral Presentation</td>
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<td>Special Interest Group Symposium 1</td>
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<td>16:30-16:50</td>
<td>Nonalcoholic Fatty Liver Disease (NAFLD): Non-obese NAFLD Patients</td>
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<td>Difference between Western and Eastern NAFLD Patients</td>
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<td>17:10-17:30</td>
<td>Clinical Differences between Obese and Non-obese NAFLD Patients</td>
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<td>17:30-17:50</td>
<td>Therapeutic Approach in Non-obese NAFLD Patients</td>
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<td>17:50-18:10</td>
<td>Hepatic Lipid and Glucose Metabolism in NAFLD</td>
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### WEST TOWER

**Room C [B1]**

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<th>Time</th>
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<tr>
<td>13:10-14:40</td>
<td>Health Policy Forum.</td>
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<tr>
<td>13:10-13:25</td>
<td>Clinician’s Perspective on Current Status and Emerging Strategies for Management in Alcoholic Liver Diseases</td>
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<tr>
<td>13:25-13:40</td>
<td>Journalist’s Perspective on Current Status and Emerging Strategies for Management in Alcoholic Liver Diseases</td>
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<tr>
<td>13:40-13:55</td>
<td>Jurist’s Perspective on Current Status and Emerging Strategies for Management in Alcoholic Liver Diseases</td>
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<td>13:55-14:10</td>
<td>Public Health Politician’s Perspective on Current Status and Emerging Strategies for Management in Alcohol-related Health Problems</td>
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<tr>
<td>14:10-14:40</td>
<td>Panel Discussion</td>
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### EAST TOWER  
**Room A [2F]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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</thead>
</table>
| 08:30-09:50| **KLTS Symposium 1**  
How to Minimize Living Donor’s Damage and Maximize Living Donor’s Safety? **PKI**  
Hee Jung Wang (Ajou Univ.), Soon Il Kim (Yonsei Univ.) |                                                                                   |
| 08:30-09:50| Intra-operative Management for Donor Safety during Laparoscopic Donor Hepatectomy | Choon Hyuck David Kwon, Sungkyunkwan Univ.                               |
| 09:00-10:00| Early Experience of Robotic Donor Hepatectomy: Learn from Pioneer        | Gi Hong Choi, Yonsei Univ.                                                |
| 09:30-09:50| Fate of Live Donor after Liver Donation: Physician’s View              | Dong Hyun Sinn, Sungkyunkwan Univ.                                        |
| 09:30-09:50| Coffee Break                                                            |                                                                           |
| 10:10-12:10| **KLTS Symposium 2**  
How Far Extended Criteria for Advanced Hepatocellular Carcinoma in Liver Transplantation? **PKI**  
Joo-Seop Kim (Hallym Univ.), Hee Chun 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.                                           |
| 11:22-11:46| Adjunct 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]**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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| 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) |                                                                                   |
| 08:30-09:50| 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, KAST                                                      |
| 09:10-09:30| New Therapeutic Perspectives for Hepatitis B Virus Cure                 | Jio-Horng Koo, 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                                     |
| 10:30-11:00| 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]**

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

### EAST TOWER

**Room D [2F]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>07:00-08:00</td>
<td>Early Morning Workshop 1 (^{TM}) [HBV] Unsolved Issues in the Management of Chronic Hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Young-Suk Lim (Univ. of Ulsan), Hyung Joon Yim (Korea Univ.)</td>
</tr>
</tbody>
</table>

### EAST TOWER

**Room E [2F]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>07:00-08:00</td>
<td>Early Morning Workshop 2 [HCV] Anti-HCV Treatment for Special Population</td>
</tr>
<tr>
<td></td>
<td>Maria Bui (Hospital Universitari Vall d'Hebron), Otodor Baatarkhuu (Mongolian National Univ. of Medical Sciences), Chang Wook Kim (The Catholic Univ. of Korea), Geum-Youn Gwak (Sungkyunkwan Univ.)</td>
</tr>
</tbody>
</table>

### WEST TOWER

**Room F [2F]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:10-14:10</td>
<td>KLTS Coordinator Session (^{TM})</td>
</tr>
<tr>
<td></td>
<td>Hea Seon Ha (Asan Medical Center), Bak Nyeo Kim (Samsung Medical Center)</td>
</tr>
<tr>
<td>13:10-13:25</td>
<td>Preoperative Evaluation of Living Donor Candidate for</td>
</tr>
<tr>
<td></td>
<td>Liver Transplantation</td>
</tr>
<tr>
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<td>Sanghee Song, Seoul National Univ. Hospital</td>
</tr>
<tr>
<td>13:25-13:40</td>
<td>Education and Counselling for Living Donor for Liver</td>
</tr>
<tr>
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<td>Transplantation</td>
</tr>
<tr>
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<td>Sunyoung Son, Gangnam Severance Hospital</td>
</tr>
<tr>
<td></td>
<td>Ji Yeon Park, Seoul St. Mary’s Hospital</td>
</tr>
<tr>
<td>13:55-14:10</td>
<td>Immuno Suppression after Liver Transplantiation</td>
</tr>
<tr>
<td></td>
<td>Jeong Hee Kang, Pusan National Univ. Yangsan Hospital</td>
</tr>
<tr>
<td>Time</td>
<td>Room AB</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>08:00</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>Symposium 2 Pros &amp; Cons of LC-Controversial Issues (08:30-09:30)</td>
</tr>
<tr>
<td>09:30</td>
<td>KHBPS-KLTS Joint Symposium (08:30-09:30)</td>
</tr>
<tr>
<td>10:00</td>
<td></td>
</tr>
<tr>
<td>10:00</td>
<td></td>
</tr>
<tr>
<td>10:10</td>
<td>Plenary Session 2 (10:10-12:10)</td>
</tr>
<tr>
<td>11:00</td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td>Luncheon Symposium 6 (by Gilead) (12:10-13:10)</td>
</tr>
<tr>
<td>13:00</td>
<td></td>
</tr>
<tr>
<td>13:00</td>
<td>Special Lecture 2 (13:10-14:10)</td>
</tr>
<tr>
<td>14:00</td>
<td></td>
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<tr>
<td>15:00</td>
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</tr>
<tr>
<td>16:00</td>
<td></td>
</tr>
<tr>
<td>16:00</td>
<td>Free Paper 11 Surgery (16:30-17:40)</td>
</tr>
<tr>
<td>17:00</td>
<td></td>
</tr>
<tr>
<td>17:00</td>
<td>Closing &amp; Award Ceremony (17:40-18:00)</td>
</tr>
<tr>
<td>Time</td>
<td>Session/Panel</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
</tr>
<tr>
<td>08:30-09:50</td>
<td>Symposium 2</td>
</tr>
<tr>
<td>08:30-08:50</td>
<td>Nonselective Beta Blocker: Hemodynamic Effects vs. Non-hemodynamic Effects</td>
</tr>
<tr>
<td>08:50-09:10</td>
<td>Scoring Systems for Alcoholic Hepatitis</td>
</tr>
<tr>
<td>09:10-09:30</td>
<td>Anticoagulation: Do or Avoid?</td>
</tr>
<tr>
<td>09:30-09:50</td>
<td>Albumin: New Roles beyond Volume Expander</td>
</tr>
<tr>
<td>09:50-10:10</td>
<td>Coffee Break</td>
</tr>
<tr>
<td>10:10-12:10</td>
<td>Plenary Session 2</td>
</tr>
<tr>
<td>12:10-13:10</td>
<td>Luncheon Symposium 6 [by Gilead]</td>
</tr>
<tr>
<td>13:10-13:40</td>
<td>Special Lecture 2</td>
</tr>
<tr>
<td>13:10-13:40</td>
<td>Special Lecture 2</td>
</tr>
<tr>
<td>13:50-15:10</td>
<td>The Diagnosis of Acute Kidney Injury in Cirrhosis:</td>
</tr>
<tr>
<td>13:50-14:10</td>
<td>The Reasonable Cut-off Serum Creatinine Value</td>
</tr>
<tr>
<td>14:10-14:30</td>
<td>The Current Management of Acute Kidney Injury in Cirrhosis</td>
</tr>
<tr>
<td>14:30-14:50</td>
<td>Role of Heart in Refractory Ascites, Acute Kidney Injury, and Hepatorenal Syndrome</td>
</tr>
<tr>
<td>14:50-15:10</td>
<td>The Liver in Cardiac Disease</td>
</tr>
<tr>
<td>15:30-16:30</td>
<td>Coffee Break &amp; Poster Oral Presentation</td>
</tr>
<tr>
<td>17:40-18:00</td>
<td>Closing &amp; Award Ceremony</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Panel</th>
<th>Description</th>
<th>Location/Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30-09:50</td>
<td>KHBPS-KLTS Joint Symposium</td>
<td>How Can We Overcome Complicated Portal Vein?</td>
<td>Dong Goo Kim (The Catholic Univ. of Korea), Joo-Won Joh (Sungkyunkwan Univ.)</td>
</tr>
<tr>
<td>08:30-08:50</td>
<td>Indication or Contraindication of Liver Transplantation in Patient with Portal Vein Thrombosis</td>
<td>Nam-Joon Yi, Seoul National Univ.</td>
<td></td>
</tr>
<tr>
<td>08:50-09:10</td>
<td>Anatomical Reconstruction</td>
<td>Gyu-Seong Choi, Sungkyunkwan Univ.</td>
<td></td>
</tr>
<tr>
<td>09:10-09:30</td>
<td>How to Overcome Complicated Portal Vein Thrombosis? Extra-anatomic Bypass</td>
<td>Dek-Bog Moon, Univ. of Ulsan</td>
<td></td>
</tr>
<tr>
<td>09:30-09:50</td>
<td>Intervention for Complicated Portal Vein</td>
<td>Gi-Young Ko, Univ. of Ulsan</td>
<td></td>
</tr>
<tr>
<td>09:50-10:10</td>
<td>Coffee Break</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:10-13:10</td>
<td>Luncheon Symposium 7 [by Novartis]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### WEST TOWER

**Room C [B1]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:10-14:10</td>
<td><strong>KHBPS-JSHBPS Joint Symposium 1</strong> Evidence Based Management for Hepatocellular Carcinoma</td>
<td>Norhiro Kokudo (The Univ. of Tokyo), Hee Jung Wang (Ajou Univ.)</td>
</tr>
<tr>
<td>13:10-13:30</td>
<td>Primary Liver Cancer Registry in Japan: How Has It Been Evolving?</td>
<td>Norhiro Kokudo, The Univ. of Tokyo</td>
</tr>
<tr>
<td>13:30-13:50</td>
<td>Random Sampling of Korea Central Cancer Registry for Hepatocellular Carcinoma</td>
<td>Young-Suk Lim, Univ. of Ulsan</td>
</tr>
<tr>
<td>14:10-15:30</td>
<td><strong>KHBPS-JSHBPS Joint Symposium 2</strong> Incorporating Recent Technologies in Liver Surgery</td>
<td>Atsushi Sugioka (Fujita Health Univ.), Dong-Sup Yoon (Yonsei Univ.)</td>
</tr>
<tr>
<td>14:10-14:30</td>
<td>Laparoscopic and Robotic Liver Resection</td>
<td>Atsushi Sugioka, Fujita Health Univ.</td>
</tr>
<tr>
<td>14:30-14:50</td>
<td>Laparoscopic Liver Resection Using 3D Camera System</td>
<td>Kyung-Suk Suh, Seoul National Univ.</td>
</tr>
<tr>
<td>14:50-15:10</td>
<td>Application of Indocyanine Green Fluorescence Imaging in Liver Resection</td>
<td>Norhiro Kokudo, The Univ. of Tokyo</td>
</tr>
<tr>
<td>15:10-15:30</td>
<td>Liver Resection Using Robotic System</td>
<td>Gi Hong Choi, Yonsei Univ.</td>
</tr>
<tr>
<td>15:30-16:30</td>
<td>Coffee Break &amp; Poster Oral Presentation</td>
<td></td>
</tr>
</tbody>
</table>

### EAST TOWER

**Room AB [2F]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30-09:50</td>
<td><strong>Symposium 3</strong> Nonalcoholic Fatty Liver Disease</td>
<td>Jaung-II Lee (Kyung Hee Univ.), Seung Kew Yoon (The Catholic Univ. of Korea)</td>
</tr>
<tr>
<td>08:30-08:50</td>
<td>Lipid Droplet as a Potential Target for Nonalcoholic Fatty Liver Disease</td>
<td>Douglas Mashek, Univ. of Minnesota</td>
</tr>
<tr>
<td>08:50-09:10</td>
<td>Noninvasive Diagnostic Method of Nonalcoholic Steatohepatitis</td>
<td>Fuji Miyoshi, Osaka Univ.</td>
</tr>
<tr>
<td>09:10-09:30</td>
<td>Hepatocellular Carcinoma Development in Nonalcoholic Fatty Liver Disease</td>
<td>Luca Valenti, Universita degli Studi di Milano</td>
</tr>
<tr>
<td>09:30-09:50</td>
<td>Molecular Targets for Nonalcoholic Steatohepatitis Therapeutics</td>
<td>Yong Kyun Cho, Sungkyunkwan Univ.</td>
</tr>
</tbody>
</table>

### EAST TOWER

**Room DE [2F]**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>07:00-08:20</td>
<td>Breakfast Workshop [by Bayer]</td>
</tr>
</tbody>
</table>
Contents

Plenary Session 1

PS 1-1 Virus-induced IFN-γ4 Potently Blocks IFN-α Signaling by ISG15/USP18 in HCV Infection: Implication for Increased IFN Responsiveness after DAA Treatment
PI Sook Sung, Seon-Hui Hong, Su-Hyung Park, Eun-Cheol Shin
3

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
3

PS 1-3 Daclatasvir Plus Sofosbuvir ± Ribavirin for Treating Chronic HCV Infection in Patients with Advanced Liver Disease: European compassionate Use Program Results
4

PS 1-4 Prospective Comparison between TE, SSI, and ARFI for Predicting Fibrosis in Subjects with NAFLD
Won Kim, Myoung Seok Lee, Jung Ho Kim
4

PS 1-5 The Functional Impact of HBV Integration into the Telomerase Reverse Transcriptase Promoter on Hepatocarcinogenesis
Jeong Won Jang, Abdul M. Oseini, Yang Li, Catherine D. Moser, Karl J. Clark, Lewis R. Roberts
5

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, Won Hyeok Choe, Dong Hyun Shin, Jeong-Hoon Lee, Joon Yeul Nam, Hye Ki Cho, Young Youn Cho, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon
5

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 Kyung Hong, Hyo-Sik Kim, Hye Young Kim, Youngroh Cho, Kwang-Hoo Lee, Kyung-Suk Suh
6

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, Seung Ho Choi, Tae Ho Hong, Young Kyoung You, Dong Goo Kim
6

Plenary Session 2

PS 2-1 A Phase 3 Study of Tenofovir Alafenamide Compared with Tenofovir Disoproxil Fumarate in Patients with HBeAg-negative, Chronic Hepatitis B
Young-Suk Lim, Shi-Hyun Bae, Sang Hoon Ahn, Hyung Joon Kim, Won Young Tak, Kwan Sik Lee, Maria But, Edward Gan, Wai Kay Seto, Herry LY Chan, Wan Long Chuang, Tatjana Stupanova, Arijit Das, Raj Mehta, Harry Janssen, SK Acharya, John F Flaherty, Benedetta Masotto, Andrea Cathcart, Philip Dinh, G Mani Subramanian, John G McHutchison, Calvin Pan, Mauricio Brunetto, Namki Ibumi, Patrick Marcellin
11

PS 2-2 Entecavir versus Lamivudine for Prevention of Liver-related Events in Patients with HBV-related Advanced Liver Disease: A Multicenter, Prospective Study
Jun Yong Park, Sang Gyun Kim, Won Young Tak, Hyung Joon Yim, Byoung Kuk Jag, Moon Young Kim, Byung B Kim, Jin-Woo Lee, Ki Tae Yoon, Jae Youn Cheong, So Young Kwon, Tae Yeol Kim, Si Hye Bae, Yeon Seok Soo, Jeung Hyon Kwon, Dong Joon Kim, Ja-Kyung Kim, Soo Jung Won, Jeong Yoon Jang, Jung Hyun Lee, Kwang-Hoon Han, for the SOLL Study Group Department of Internal Medicine
11

PS 2-3 Risk of Overestimation of Renal Function Using Estimated GFR in Patients with Liver Cirrhosis
Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim, Bora Lee, Sang Woon Jeong, Jae Young Jang, Sae Hwan Kim, Hong Soo Kim, Young Don Kim, Gab Jin Cheon, Boo Sung Kim
12

PS 2-4 New Paper Pencil Test for the Diagnosis of Minimal Hepatic Encephalopathy in Liver Cirrhosis Patients in Korea
Jae Yoon Jeong, Dae Won Jun, Dasei Bae, Joo Hyun Son, Chang Hong Lee
12

PS 2-5 Blocking Energy Metabolism by Hexokinase II Inhibitor Overcomes Sorafenib Resistance via Augmenting Endoplasmic Reticulum Stress in Hepatocellular Carcinoma
Jeong-Ju Yoo, So Jong Yu, Jun Na, Kyung Min Kim, Young Yoon Cho, Hye Ki Cho, Dong Hyun Lee, Eun Ju Cho, Jeong Hoon Lee, Yoon Jun Kim, Chung Yang Kim, Hyewon Yoon, Jung-Hwan Yoon
13

PS 2-6 TonEBP Promotes Hepatocellular Carcinoma via Promotion of Inflammation
Jun Ho Lee, Neung Hee Park, Hwan Jee Kang, Jae Hee Suh, Chang Jae Kim, Hwan Hee Lee, Soo Young Cho, Whaeseon Lee-Kwon, Hye Moo Kwon
13

PS 2-7 EDN1 Expression as a Novel Biomarker for Predicting Sorafenib Responsiveness in Patients with Hepatocellular Carcinoma
14
<table>
<thead>
<tr>
<th>Free Paper Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. HBV, Clinical</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-001</th>
<th>Early Hepatitis B Surface Antigen Seroclearance after Commencement of Antiviral Treatment in Patients with De Novo HBV Reactivation</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hye-young Kim, Sung-Woo Ahn, Suk Kyun Hong, Kyung Chul Yoon, Hye-Sin Kim, Jin Yong Choi, Youngrok Choi, Hae Won Lee, Nam-Joon Yi, Kwang-Woong Lee, Kyung-Suk Suh, Korea Central Cancer Registry, The Korean Liver Cancer Study Group</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>O-002</th>
<th>Telbivudine versus Entecavir in Entecavir-Treated Patients with Undetectable Hepatitis B Virus DNA: Randomized Trial</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jihyun An, Young-Suk Lim, Gai-Ae Kim, Hyung Don Kim, Seong-bong Han, Danbi Lee, Ju Hyun Shim, Han Chul Lee, Yong Sang Lee</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-003</th>
<th>Long-term Nucleotide Analogue Treatment Has Increase of Renal Toxicities Compared to Entecavir Treatment in Patients with Chronic Hepatitis B</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young Youn Cho, Eun Ji Cho, Young Chang, Joon Yool Nam, Hyo-ki Cho, Seong Hee Kang, Jeong-Hoon Lee, Su Jong Yi, Jung-Hwan Yoon, Yoon Jun Kim</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-004</th>
<th>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</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Namyoung Paik, Dong Hyeon Sihn, Jung Hee Kim, Won-seok Kang, Geum-youn Giwak, Yang-Han Paik, Moon Seok Choi, Joon Hyo-won Koh, Kwang-Heul Han, Jung Yoon Park</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-005</th>
<th>Comparison of Clinical Outcomes of Antiviral Treatment in Compensated Liver Cirrhosis: Entecavir vs. Tenofovir</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jeong Eun Song, Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Jun Yong Park</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-006</th>
<th>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</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young Min Shin, Kyung Hye Park, Seok Won Jung, Neung Hwa Park, Bo Kyung Park, Chang Jae Kim, Byung Uk Lee, Jae Ho Park, Byung Gu Kim, In Du Jeong, Sung-Jo Bang, Jung Woo Shin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-007</th>
<th>Hepatitis B Surface Antigen Titer Is a Good Indicator of Durable Viral Response after Off-treatment of Entecavir for Chronic Hepatitis B</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Han Ah Lee, Seung Woon Park, Sang Jung Park, Tae Hyung Kim, Sang Jun Suh, Young Kul Jung, Hye Hoon Kim, Hyeon Jo Yoon, Kwan Soo Byun, Soon Hwa Um, Yeon Seok Seo</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-008</th>
<th>Change in Alpha-fetoprotein Levels in Chronic Hepatitis B Patients on Tenofovir Therapy</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chung Seep Lee, Beom Hee Kim, Sanghyuk Im, Ju Hyun Lee, Jang Wha Chung, Eun Sun Jang, Sook-Hyang Jeong, Jin-Wook Kim</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-009</th>
<th>Prevention of Vertical Transmission with Antiviral Agent during Late Pregnancy in Highly Viremic Mothers Infected with Hepatitis B Virus</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kwang-E Seo, Si-Hyun Bae, Ha Lim Lee, Hee Yeon Kim, Hye Ji Kim, Pi Sool Sung, Bo Hyun Jung, Seung Kew Yoon, Jeong Won Jung, Jong Young Choi, Chung-Hwa Park, In-Yang Park, Juyeong Lee, Hyun Seung Lee, Sa-In Kim, U Im Chang, Chang Wook Kim, Se Hyun Yo, Young Lee, Jong-Hyun Kim</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-010</th>
<th>Tiny Echogenic Nodule (TEN) Detected in High-frequency Spatial Compound Ultrasonography Is a New Specific Image Marker for Chronic Hepatitis B Virus Infection</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young Min Park, Won San, Son Hyeong Yoo, Sang Jung Park</td>
<td></td>
</tr>
</tbody>
</table>

| **2. HCV, Clinical**    |

<table>
<thead>
<tr>
<th>O-011</th>
<th>Establishment of Full Genomic Length Resistance-Associated Variant Genotype 2 Hepatitis C Viruses and Applications for Future Therapeutic Strategies</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyung Joon Yim, Billy Lin, Shanghane He, Zongyi Hu, T. Jake Liang</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-012</th>
<th>Asian Patients with Genotype 1 HCV Achieve 99% SVR with 12 Weeks of Ledipasvir/Sofosbuvir: Integrated Analysis of Phase 3 Studies</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young-Suk Lim, Sang Hoon Ahn, Kwan Sik Lee, Seung Woon Paik, Youn-Jae Lee, Sook-Hyang Jeong, Jo-Hyun Kim, Seung Kew Yoon, Hyung Joon Yim, Won Young Tak, Sang-Young Han, Jenny C. Yang, Shampa De-Dertel, Hongmei Mo, Bing Gao, Yoon Jun Kim, Kwan Soo Byun, Young Seok Kim, Seong Hee Kang, Jeong Hee, Ja-Hong Kao, Wan-Long Chuang, Masashi Mizokami, Masa Oomata, Kwang-Hyub Han</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-013</th>
<th>Asian Patients with Genotype 2 HCV Achieve 98% SVR with Sofosbuvir and Ribavirin: Integrated Analysis of Phase 3 Studies</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sang Hoon Ahn, Young-Suk Lim, Kwan Sik Lee, Seung Woon Paik, Youn-Jae Lee, Sook-Hyang Jeong, Jo-Hyun Kim, Seung Kew Yoon, Hyung Joon Yim, Won Young Tak, Sang-Young Han, Jenny C. Yang, Shampa De-Dertel, Hongmei Mo, Bing Gao, Yoon Jun Kim, Kwan Soo Byun, Young Seok Kim, Seong Hee Kang, Jeong Hee, Ja-Hong Kao, Wan-Long Chuang, Masashi Mizokami, Masa Oomata, Kwang-Hyub Han</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O-014</th>
<th>Integrated Safety and Tolerability of Dadacavir plus Asunaprevir in Patients with Chronic HCV Genotype 1b Infection</th>
<th>25</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>O-015</th>
<th>Hepatitis C Virus Genotype 3 Is Associated with the Development of Hepatocellular Carcinoma and Mortality in Patients with Cirrhosis</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sang Soo Lee, Ra Ri Cha, Chang Min Lee, Wan Soo Kim, Hye Chun Cho, Jin Joo Kim, Jin Min Lee, Hong Jun Kim, Chang Yoon Ha, Hyun Jeon Kim, Tae Hyo Kim, Woon Tae Jung, Ok Jae Lee</td>
<td></td>
</tr>
</tbody>
</table>
O-016 Long-term Recipient and Graft Survival after Kidney Transplantation in Recipients with Hepatitis C Virus Infection .......................... 26
Nae-Yun Heo, Prowpanga Udompap, Alytha Malaniithara, Donghee Kim, W. Ray Kim

O-017 Prevalence of Hepatitis C Virus Variants Resistant to NS5A Inhibitor in the Korean Population ............................................. 26
Seung Bum Lee, Ki Tae Yoon, Young Mi Hong, Mung Cho, Yang-Hyon Baek, Won Lim, Hyun Young Woo, Jeong Heo, Nae-Yun Heo, Sang Youn Hwang

O-018 Effect of Renal Impairment on HCV Direct Acting Antivirals Drugs (DAA) Primarily Eliminated by Metabolism or Biliary Excretion ............ 27
T. Garimella, T. Eley, M. Bilano, Y. Gandhi, F. LaCreta, R. Bertz, M. AbuTarif

O-019 High Sustained Virologic Response with Daclatasvir plus Asunaprevir in HCV GT-1b Chinese, Korean and Taiwanese without Baseline NS5A Polymorphisms ........................................................................................................................................... 27

O-020 Absence of HBV Reactivation among HCV Infected Patients with Reactive Hepatitis B Core Antibody Treated with Ledipasvir/Sofosbuvir for 12 Weeks ................................................ 28
Mark Sulikowski, Kwang-Hyub Han, Jia-Hong Kao, Jenny C. Yang, Bing Gao, Diana M. Brainard, Wan-Long Chuang, Edward J. Gane

3. NAFLD, Clinical

O-021 Prospective Comparison and Subgroup Analysis of Noninvasive Fibrosis Assessment to Predict Advanced Fibrosis or Cirrhosis in Non-alcoholic Fatty Liver Disease .............................................................. 28
Sae Kyung Joo, Byeong Gwan Kim, Won Kim

O-022 The Accuracy of Transient Elastography and Comparison of Non-invasive Markers for Assessing Fibrosis in Korean Patients with Nonalcoholic Fatty Liver Disease ........................................................................ 29
Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Do Young Kim, Sung Hoon Ahn, Young Nyun Park, Kwang-Hyub Han, Jun Yong Park

O-023 Assessment of Change of Intrahepatic Fat Amount Using Controlled Attenuation Parameter in Clinical Trial ........................................ 29
Sang Bong Ahn, Dae Won Sun, Jae Yoon Jeong, Joo Hyun Sohn, Chang Hong Lee

O-024 Relationship between Appendicular Sarcopenia and Non-alcoholic Fatty Liver Disease in Korean Population ................................. 30
Sae Kyung Joo, Koo Bo Kyung, Won Kim

O-025 Computer-aided Relative Scoring of Fatty Liver Intensity in High Frequency 9 MHz Ultrasound Image: A Feasibility Study ......................... 30
Young Min Park, Won Son, Sun Hong Yoo, Sang Jong Park

O-026 The Impact of Controlled Attenuation Parameter on Liver Stiffness Measurement Using Transient Elastography in Patients with Non-alcoholic Fatty Liver Disease ................................................................. 31
Dong Hyeon Lee, Won Kim, Sae Kyung Joo, Yong Jin Jung, Byeong Gwan Kim, Kook Jae Lee

O-027 Risk of Hepatocellular Carcinoma in Korean Patients with Metabolic Syndrome: A Big Data Analysis .......................... 31
Miraon Ki, Hea Young Cha, Bo Hyun Kim, Jong-Won Park

O-028 Noninvasive Fibrosis Markers are Associated with Coronary Artery Calcification in Nonalcoholic Fatty Liver Disease ......................... 31
Do Seon Song, U. Im Chang, Ji Hee Kim, Ki Dong Yoo, Koon Woong Moon, Dong Gyu Moon, Jin Mo Yang

O-029 Nonalcoholic Fatty Liver Disease and Progression of Coronary Artery Calcification: A Cohort Study ................................................................. 32
Dong Hyun Sinn, DaeBee Kang, Yoo-Soa Chang, SeungHo Ryu, SeonHyu Gw, HyunKyungyoung, DongHyung Seang, Soo Jin Cho, Byoung-Kee Yi, Hyung-Doo Park, Seung Woon Paik, Young Bae Seo, Mariana Lazo, Joao A. C. Lima, Eilse Gueller, JeeHye Cho, Geum-Youn Gwak
### 5. HCV, Clinical

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>36</td>
</tr>
<tr>
<td>O-041 Clinical Characteristics of HBV/HCV Co-infection Over HCV Mono-infection Based on a Real-life Cohort</td>
<td>38</td>
</tr>
<tr>
<td>O-040 High Therapeutic Efficiency of LDV/SOF in Asian Patients with CHC Genotype 1b Infection</td>
<td>37</td>
</tr>
<tr>
<td>O-039 The Experience of Daclatasvir and Asunaprevir Treatment in Korean Patients with Hepatitis C Genotype 1b Infection</td>
<td>37</td>
</tr>
<tr>
<td>O-038 How Many Chronic Hepatitis C Patients Would Be Treated More in DAA Era?</td>
<td>38</td>
</tr>
<tr>
<td>O-037 Chronic Hepatitis B Infection and Non-hepatocellular Cancers: A Hospital Registry-Based, Case-control Study</td>
<td>36</td>
</tr>
<tr>
<td>O-036 A Comparison between Transient Elastography and FIB-4 to Assess the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B</td>
<td>36</td>
</tr>
<tr>
<td>O-035 Switching to Tenofovir versus Continuing Entecavir in Chronic Hepatitis B Patients with Partial Virologic Response During Entecavir Therapy: STEEP Study</td>
<td>35</td>
</tr>
<tr>
<td>O-034 Efficacy and Safety of Tenofovir DF (TDF) in Chronic Hepatitis B Patients (CHB) with Lamivudine Resistance (LAM-R): 5-year Results</td>
<td>35</td>
</tr>
<tr>
<td>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: A Randomized Trial</td>
<td>34</td>
</tr>
</tbody>
</table>

### 6. Liver Cirrhosis, Clinical

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-048 Daclatasvir plus Asunaprevir for Chronic Hepatitis C Virus Genotype 1b Infection: Real Life Data in Korea</td>
<td>41</td>
</tr>
<tr>
<td>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</td>
<td>41</td>
</tr>
<tr>
<td>O-046 Incidence, Epidemiological Characteristics and Transmission of Sharp Injury in Health Care Workers in a Korean University Hospital during 2011-2015</td>
<td>40</td>
</tr>
<tr>
<td>O-045 Analysis of the Efficacy and Safety of Daclatasvir and Asunaprevir in Korean Genotype 1b Chronic Hepatitis C Patients</td>
<td>40</td>
</tr>
<tr>
<td>O-044 ONXY-I: Efficacy of Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir in South Korean and Taiwanese Patients with HCV Genotype 1b Infection and without Cirrhosis</td>
<td>39</td>
</tr>
<tr>
<td>O-043 Daclatasvir plus Asunaprevir in Interferon (a) Ribavirin-Ineligible/Intolerant Asian Patients with Chronic Hepatitis C Genotype 1b Infection</td>
<td>39</td>
</tr>
<tr>
<td>O-042 How Many Chronic Hepatitis C Patients Would Be Treated More in DAA Era?</td>
<td>38</td>
</tr>
<tr>
<td>O-041 Clinical Characteristics of HBV/HCV Co-infection Over HCV Mono-infection Based on a Real-life Cohort</td>
<td>38</td>
</tr>
<tr>
<td>O-040 High Therapeutic Efficiency of LDV/SOF in Asian Patients with CHC Genotype 1b Infection</td>
<td>37</td>
</tr>
<tr>
<td>O-039 The Experience of Daclatasvir and Asunaprevir Treatment in Korean Patients with Hepatitis C Genotype 1b Infection</td>
<td>37</td>
</tr>
<tr>
<td>O-038 How Many Chronic Hepatitis C Patients Would Be Treated More in DAA Era?</td>
<td>38</td>
</tr>
<tr>
<td>O-037 Chronic Hepatitis B Infection and Non-hepatocellular Cancers: A Hospital Registry-Based, Case-control Study</td>
<td>36</td>
</tr>
<tr>
<td>O-036 A Comparison between Transient Elastography and FIB-4 to Assess the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B</td>
<td>36</td>
</tr>
<tr>
<td>O-035 Switching to Tenofovir versus Continuing Entecavir in Chronic Hepatitis B Patients with Partial Virologic Response During Entecavir Therapy: STEEP Study</td>
<td>35</td>
</tr>
<tr>
<td>O-034 Efficacy and Safety of Tenofovir DF (TDF) in Chronic Hepatitis B Patients (CHB) with Lamivudine Resistance (LAM-R): 5-year Results</td>
<td>35</td>
</tr>
<tr>
<td>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: A Randomized Trial</td>
<td>34</td>
</tr>
</tbody>
</table>
7. Liver Transplantation

O-059 Factors Associated with Worse Outcome in Korean Split-liver Transplantation: Analysis of the 10-year Korean Network for Organ Sharing Data Base
Nam-Joon Yi, Sanghee Song, Ok-Kyung Kim, Hyeyoung Kim, Suk Kyun Hong, Hyo-Suk Kim, Youngrok Choi, Eun Sun Jung, Yong Man Kim, Sooin Seo, Kwang-Woong Lee, Seung Cheol Oh, Min Young Park, Sohee Kim, Nam-Joon Yi, Sang-Jun Suh

O-060 Renal Function Difference between Anti-hepatitis B Immunoglobulin(HBIG) Monotherapy and HBIG Combined with Entecavir
Jae Geun Lee, Jung Jun Lee, Seung Hwan Song, Jae Youn Lee, Su-kyung Kwon, Myoung Soo Kim, Min Ki Je, Gi Hong Choi, Jin Sub Choi, Soon Il Kim, Dong Jin Joo

O-061 Hepatitis B Virus Immunoglobulin Is Internalized in Hepatocytes via Endocytosis and Induce Auto-phagosome
Soon Seo, Kwang-Woong Lee, Seung Cheol Oh, Min Young Park, Sohee Kim, Nam-Joon Yi, Kyung-Suk Suh

O-062 Re-endothelialization of Decellularized Porcine Liver Prevent Thrombosis
Jong Man Kim, Jisoo Lee, Kyung-Suk Suh, Nuni Lee, Chon-Woo Cho, Gyu-Seong Cho, Choon Hyuck David Kwon, Jae-Won Joh

O-063 Oncologic Outcomes of ABO-incompatible Living Donor Liver Transplantation for HCC Patients
Jae Youn Lee, Su-Kyung Kwon, Seung Hwan Song, Jae Geun Lee, Juhan Lee, Myoung Soo Kim, Gi Hong Choi, Jin Sub Choi, Eun Sun Jung, Soon Il Kim, Dong Jin Joo

O-064 Clinical Usefulness of mRECIST Embolometrica for Recurrence Estimation of Hepatocellular Carcinoma in Living Donor Liver Transplantation
Chun Woon Cho, Meshal Saleh Aldosri, Nasser Alzerwi, Kyeong Sik Kim, Seounghyun Kim, Jae-Soo Lee, Jonghwan Lee, Nuni Lee, Choon Hyuck David Kwon, Jong Man Kim, Gyu-Seong Cho, Jae-Won Joh

O-065 Results of Living Donor Age of Sixth Decade for Adult Liver Transplantation Using a Right Lobe Graft
Seok-Hwan Kim, Shin Hwang, Tae-Yong Ha, Da Hyun Jung, Sung-Hyun Kim, Chul-Soo Ahn, Deok-Bog Moon, Ki-Hun Kim, Gil-Chun Park, Kwang-Ho Baik, Dong Jin Joo

O-066 Efficacy of Rabbit Anti-thymocyte Globulin for Steroid-resistant Acute Rejection after Liver Transplantation
Jae Geun Lee, Juhan Lee, Jung Jun Lee, Seung Hwan Song, Min Ki Je, Gi Hong Choi, Myoung Soo Kim, Jin Sub Choi, Soon Il Kim, Dong Jin Joo

8. HCC, Basic

O-067 Modified AS1411 Aptamer Suppresses Hepatocellular Carcinoma by Up-regulating Galectin-14
Hyeki Cho, Yun Bin Lee, Yun Cho, Jeong-Hoon Lee, Dong Hyeon Lee, Jeong-Ju Yoo, Young Youn Cho, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jong In Kim, Jong Hun Im, Jong Hwan Lee, Eun Ju Oh, Jung-Hwan Yoon
### Contents

| O-087 | CXCL10 Is Produced in Hepatitis A Virus-infected Cells in an IRF3-dependent but IFN-independent Manner | ................................................. 61 |
| O-088 | Suppression of ADH3 Inhibit Hepatic Fibrogenesis by Modulating Cellular Interactions | ................................................. 61 |
| 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 | ................................................. 61 |
| O-090 | Human Placenta-Derived Mesenchymal Stem Cells Restore Hepatic Lipid Metabolism in the Rat Bile Duct Ligation Model | ................................................. 62 |
| O-091 | Exosome Derived from Palmitic Acid-treated Hepatocytes Activates Hepatic Stellate Cells | ................................................. 62 |
| O-092 | Activating Transcription Factor 3 Is a Targeted Molecule Linking Hepatic Steatosis to Type 2 Diabetes | ................................................. 63 |
| O-093 | The Inhibitory Effect of Lorcaserin on Non Alcoholic Fatty Liver Disease in Animal Model | ................................................. 63 |
| O-094 | HNF4α as Therapeutic Agents for Non-alcoholic Fatty Liver Disease Changing with Bile Acid Metabolism | ................................................. 64 |
| O-095 | The Combined Effect of Stem Cell Factor and Granulocyte Macrophage Colony-stimulating Factor Administration after 90% Partial Hepatectomy in Rats | ................................................. 64 |

### 11. Surgery

| O-096 | Extrahepatic Glissonian Pedicle Approach in Laparoscopic Anatomical Liver Resection: A Single Institutional Early Experience | ................................................. 64 |
| O-097 | Totally Laparoscopic Right Hepatectomy in HCC Patients with Portal Vein Anomaly | ................................................. 65 |
| O-098 | Comparative Short-term Outcomes of Laparoscopic Anatomical Liver Resection for the Centrally Located Tumor: Case-matched Study with Propensity Score Matching | ................................................. 65 |
| O-099 | Prospective Randomize Control Study of Clinical Usefulness of Prophylactic Antibiotics Therapy in Laparoscopic Cholecystectomy | ................................................. 66 |
| O-100 | Outcome of Transduodenal Surgical Ampullectomy for Ampullary Neoplasms | ................................................. 66 |
| O-101 | Attenuated Role of Neoadjuvant Concurrent Chemoradiotherapy in Resectable Uncinate Process Pancreatic Cancer | ................................................. 67 |

### 12. Liver Cirrhosis, HCC

| O-102 | The Prevalence of Osteoporosis in Alcoholic Cirrhotic Patients: A Multicenter Study in Gangwon Province, South Korea | ................................................. 67 |
| O-103 | Changes in the Cardiac Varices after Eradication of Esophageal Varices by Band Ligation | ................................................. 67 |
| O-104 | Effects of Splanchnic Vasoactive Agents on Hepatic Functional Recovery and Regeneration in Porcine 70% Partial Hepatectomy Model | ................................................. 68 |
| O-105 | Hemorrhological Alteration in Patients Clinically Diagnosed with Chronic Liver Diseases | ................................................. 68 |

www.theliverweek.org  xix
O-109 Characteristics of First Diagnosed Hepatocellular Carcinoma in Liver Cirrhotic Patients during 15 Years: Multicenter Retrospective Study in Daegu-Gyeongbuk Province
Wang Young Cho, Won Jin Chung, Byung Kuk Jung, Jae Seok Hwang, Sang Jin Kim, Heon Ju Lee, Moon Soo Hwang, Young Oh Kweon, Won Young Tak, Soo Young Park, Su Hyun Lee, Chang Heeong Lee, Byung Seok Kim, Si Hye Kim, Jeong Il Suh, JunGi Park, Daegu-Gyeongbuk Liver Study Group

O-110 Risk Assessment of Developing Hepatocellular Carcinoma Using Wisteria Floribunda Agglutinin-positive Human Mac-2 Binding Protein in Chronic Hepatitis B Patients
Ja Yoon Hee, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Hyun-Suk Kim, Seung Up Kim

O-111 The Surveillance Rate and Its Impact on Early Diagnosis and Survival of Hepatocellular Carcinoma in South Korea
Sanghyuk Im, Ju Hyun Lee, Chung Seop Lee, Beom Hee Kim, Jung Wha Chung, Eun Sun Jang, Jin-Wook Kim, Sook-Hyang Jeong

O-112 Comparison of the Incidence of Hepatocellular Carcinoma in HBV, HCV and Non-infection Groups: Population Based Cohort Study
Hwa Young Choi, Min Man

O-113 Maintained Virological Remission Should Be the Endpoint during Entecavir Monotherapy
Jung Hee Kim, Dong Hyun Sinn, Won Seok Kang, Geum-Youn Gwak, Moon Seok Choi, Joon Hyek Lee, Kwang Cheol Koh, Seung Woon Park

O-114 A Novel Biomarker-based Model for the Prediction of Response to Sorafenib and Overall Survival for Advanced Hepatocellular Carcinoma: A Prospective Cohort Study
Hwa Young Kim, Jeong-Hoon Lee, Dong Hyun Lee, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon

O-115 Low Levels of Circulating MicroRNA-26a/29a as Poor Prognostic Markers in Patients with Hepatocellular Carcinoma Who Underwent Curative Treatment
Hyo Jung Cho, Ji Sun Nam, Jae Keun Kim, Ji Hee Lee, Bohlun Kim, Hee Jung Wang, Bong Wan Kim, Jung-Dong Lee, Dae Yong Kang, Ji Hyun Kim, Yang Min Jae, Jae Chul Hwang, Sung Jae Shin, Kee Myung Lee, Soon Sun Kim, Sung Won Cho, Jae Youn Cheong

O-116 Transplantation versus Hepatectomy for Hepatocellular Carcinoma Less than 2 cm: The Experience of Ajou University Hospital
Xu-Guang Hu, Ingyu Kim, Sung yeon Hong, Mao wei, Bong-Wan Kim, Hee-Jung Wang

O-117 Comparison of Treatment Outcome between Living Donor Liver Transplantation and Sorafenib for Hepatocellular Carcinoma Patients beyond the Milan Criteria
Yuri Cho, Jeong-Hoon Lee, Dong Hyun Sinn, Won Seok Kang, Geum-Youn Gwak, Moon Seok Choi, Joon Hyek Lee, Kwang Cheol Koh, Seung Woon Park

O-118 The Comparison of Percutaneous Radiofrequency Ablation with Laparoscopic Radiofrequency Ablation on Overall Survival and Recurrence of Hepatocellular Carcinoma
Hyo Soo Eun, Gee Young Yun, Byung Seok Lee, Jae Kyu Sung, Eun Soo Seok Lee, Hee Suk Moon, Sun Hyung Kang, Jang Seok Joo, Hae Jin Shin, Seok Hyun Kim

O-119 A Multimarker Panel Predicts Complete Response after Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma
Su Jong Yu, Hyun Soo Kim, Hyun Soo Kim, Arun Sohn, Young Youn Cho, Jeong-Ju Yoo, Dong Hyun Lee, Eun Ju Cho, Jeong-Hoon Lee, Jung-Soo Kim, Tae Sung Park, Yoon Jun Kim, Chung Yang Kim, Jung-Hwan Yoon, Young Soo Kim

O-120 Outcomes of Stereotactic Ablative Radiotherapy Combined with Transarterial Chemoembolization in Hepatocellular Carcinoma
Min Young Baek, Young Hee Park, Jae Young Kang, Sang-Woo Cho, Sang Hwan Lee, Sang Geun Yoon, Sang-Woo Cho, Young Seok Kim, Young Deok Cho, Hong Soo Kim, Bao Sung Kim

O-121 The Efficacy of Radiotherapy-based Multidisciplinary Treatment in Patients with Hepatocellular Carcinoma
Seung Woon Park, Soon Ho Um, Yeon Seok Seo, Han Ah Lee, Sang Jung Park, Tae Hyung Kim

O-122 Laparoscopic Liver Resection of Hepatocellular Carcinoma with a Tumor Size Larger than 5 cm: Review of 45 Cases in a Tertiary Institution
Eunmi Gil, Choon Hyoung D. Kwon, Jong Man Kim, Gyu-Seong Choi, Jin Seok Heo, Won-tae Cho, Seung Hwan Lee, Jin Yong Choi, Mi Sook Gwak, Geum-Youn Gwak, Jae-Won Joo
Contents

**Poster Oral Presentation**

**Cell Biology and Basic**

PO-001 Establishment of Hepatoma Treatment Model Using Hepatoma Cell Spheroids ........................................ 81
Han Seul Park, Jae Young Jang, Seoung Won Jeong, Seae Hwan Lee, Sang Gyune Kim, Sang-Woo Cha, Young Seok Kim, Young Deok Cho, Hong Soo Kim, Boo Sung Kim

PO-002 Uregulation of NADPH Oxidase 4 and Oxidative Stress via TGFβ-ERK-mTOR Pathway in Transdifferentiation of Mouse Hepatic Stellate Cells ........................................ 81
Soo Jin Kim, Kyu Hee Hwang, Ji Hee Kim, Moon Young Kim, Soon Koo Baik, Seung Kuy Cha, Ranjan Das, Kyu Sang Park

PO-003 Regulation of Tumor Angiogenesis and Endothelial Mesenchymal Transition by Dickkopf-1 ........................................ 81
Sung Hoon Choi, Hyun Gyu Ju, Hyemi Kim, Jun Young Park, Beomkyung Kim, Da young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Seung Up Kim

PO-004 Increased Phosphatase of Regenerating-1 by Placental Stem Cells Promote Hepatic Regeneration in a Rat Model with Bile Duct Ligation ........................................ 82
Ji Eun Oh, Soon Koo Baik, Young Woo Eom

PO-005 1-Methyl Tryptophan Increase Cell Death of Hepatic Stellate Cells Arrested by Interferon-gamma ........................................ 82
Ji Eun Oh, Soon Koo Baik, Young Woo Eom

PO-006 MicroRNA-99a Attenuates HCV Replication through the Downregulation of Subtilisin Kexin Isozyme-1 (SKI-1) / Site-1 Protease (S1P) ........................................ 83
Eun Byul Lee, Seung Kew Youn, Jung-Hee Kim, Wonhee Hur, Sung Min Kim, Jooin Ho Lee, Dong Jo Park

**HCV, Clinical**

PO-007 Daclatasvir plus Asunaprevir Therapy in Treatment-naive and Treatment-experienced Korean Patients with Genotype 1b Chronic HCV Infection: A Single-center, Real-life Experience ........................................ 83
Keum Bok Hwang, Wonseok Kang, Dong Hyun Sim, Gyun-Youn Gwak, Yang-Han Pak, Moon Seok Choi, Jooin Hyeok Lee, Kwang Cheol Koh, Seung Woon Park

PO-008 Early Viral Response of Korean Chronic Hepatitis C Patients Treated with Daclatasvir and Asunaprevir Combination Therapy ........................................ 84
Beom Hee Kim, Chung Seop Lee, Sanghyuk Im, Ju Hyun Lee, Jong Wha Chung, Eun Sun Jung, Sook-Hyang Jeong, Jin-Wook Kim

PO-009 Effect of Baseline Resistance-associated Variants on SVR with the 3D Regimen with and without RBV in GT1a and GT1b-infected Patients ........................................ 84
Christoph Sarrazin, Mark S. Sulkowski, Preethi Krishnan, Rakesh Tripathi, Greta Schnell, Yan Xi, Daniel E. Cohen, Roger Tinh, Lino Rodrigues Jr., Yan Luo, Nancy S. Shulman, Tami Pilot-Matias, Christine Collins

PO-010 Real-life Prevalence of Resistant Associated Variants (RAV) and Early Treatment Response of Daclatasvir Plus Asunaprevir Combination Therapy ........................................ 85
Jung-Hwan Yu, Ja Kyung Kim, Jung II Lee, Kwan Sik Lee

PO-011 One of the Earliest HCV Treatment Results with Direct Acting Antiviral Agents ........................................ 85
Aymuksul Ashimkhanova, Kakharman Yesmembetov

PO-012 Efficacy of Daclatasvir + Asunaprevir for Patients with Chronic HCV Genotype 1b Infection ........................................ 86
Suk Bae Kim, Seae Hwan Lee, Tae Hye Lee, Byung Seok Lee, Hee Bok Chae, Oscar Vargas Montallegre

**Liver Cirrhosis**

PO-013 Role of New Biomarkers in Predicting AKI in Patients with Advanced Liver Cirrhosis ........................................ 86
Sang Hoon Park, Sang-Kyung Jo, Won-jong Cho, Min Sun Joo, Myoung Seok Lee

PO-014 Comparison of Prognostic Efficacy of Acute Kidney Injury Criteria in Patients with Liver Cirrhosis ........................................ 87
Tae Hyung Kim, Yeon Seok Seo, Seung Woon Park, Han Ah Lee, Sang Jung Park, Sang Juon Seo, Young Kuk Jung, Ji Hoon Kim, Hyung Joan Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um

PO-015 Baseline Renal Function Predict Hyponatremia in Liver Cirrhosis Patients Treated with Terlipressin for Variceal Bleeding ........................................ 87
Yeonmi Ju, Sung Eun Kim, Ji Won Park, Hyo Jung Su Kim, Ki Tae Suk, Young Kuk Jung, Sang Hoon Park, Myoung Seok Lee, Dong Jo Park, Choong Kee Park

PO-016 Increased Risk of Bacterial Infection in Cirrhotic Patients with Acute Variceal Bleeding Who Were Treated with Prophylactic Rifaximin ........................................ 88
Woo Kyung Yeo, Eileen L. Yoon, Hyung Gi Bae, Yu Ri Hwang, Seong Eun Park, Jong Ho Lee, Ji Young Park, Ji Min Choi, Tae Jo Jean, Won Chang Shin, Won-Choong Choi

PO-017 Cyanocrylate Injection versus Band Ligation for the Treatment of Bleeding from Cardiac Varices on Lesser Curvature Side of the Stomach ........................................ 88
Sung Jung Park, Yeon Seok Seo, Seung Woon Park, Han Ah Lee, Tae Hyung Kim, Sang Jun Seo, Young Kuk Jung, Ji Hoon Kim, Hyung Joan Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um

PO-018 Efficacy and Safety of Endoscopic Variceal Obliteration (EVO) vs. Balloon-occluded Retrograde Transvenous Obliteration (BRTO) as Prophylactic Treatment for Gastric Varices ........................................ 88
Jung Wan Choe, Hyung Joan Yim, Seae Hwan Lee, Hwan Hoon Chung, Sang Juon Seo, Young Kuk Jung, Ji Young Park, Ji Min Choi, Ji Hoon Kim, Yeon Seok Seo, Jong Eun Yeon, Sang Wook Lee, Kwan Soo Byun, Soon Ho Um

www.theliverweek.org xxii
NAFLD

PO-019  The Association between Serum Lysyl Oxidase Homolog 2 Levels and Liver Fibrosis Stages in Subjects with Non-alcoholic Fatty Liver Disease .......................... 89
Dong Hyeon Lee, Won Kim, Se Kyung Joo, Yong Jin Jung, Byeong Gwan Kim, Kook Jae Lee

PO-020  FOXA2 Overexpression Promotes Hepatic Differentiation of Adipose Tissue Derived Stem Cells ............................................................... 89
Yeon Ji Chae, Dae Won Jun, Chang Hong Lee, Jae Yoon Jeong, Jai Hyun Sohn, Ki Seok Jung, Jai Sun Lee, Hyeon Tae Kang, Ho Hyun Nam, Waqar Khalid Saeed

PO-021  The Relationship between NAFLD and the Risk of Obstructive Sleep Apnea ................................................................................................. 90
Chan Ran You, Jung Hwan Oh, Si Hyun Bae, Jong Young Cho, Seung Kew Yoon, Sang Wook Choi

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 ................................................................. 90
Min Soo Joo, Tae-Hoon Kim, Kwon-Ha Yoon, Hong Young Jun, Ki-Jong Kim, Young Hwan Lee, Myeong Su Lee, Keum Ho Choi, Ki Jung Yun, Eun Young Cho, Haek Cheoul Kim, Yong-Yeon Jeong, Chung-Hwan Jun

PO-023  Sarcopenia Is a Risk Factor for Biopsy-proven Non-alcoholic Steatohepatitis or Significant Fibrosis in Non-alcoholic Fatty Liver Disease ...................... 90
Dong Hyeon Lee, Won Kim, Bo Kyung Koo, So Kyung Joo, Jung Ho Kim, Byeong Gwan Kim

Liver Cirrhosis and Others

PO-024  S100B Expression and Interaction with the Receptor for Advanced Glycation End Products (RAGE) during Hepatofibrogenesis in Murine Model .................. 91
Ji Won Park, Mo Jong Kim, Sung Eun Kim, Yong Chul Jeong, Hai-Young Shin, Dong Joon Kim, Choong Kee Park, Eun Kyung Cho, Myeong Kuk Jang

PO-025  Risk and Outcome of Stroke in Patients with Liver Cirrhosis: Two Nationwide Studies ......................................................................................... 91
Yi-Chun Chou, Chen-Chang Liao, Chun-Chuan Shih

PO-026  Risk Factor of Post-Polypectomy Bleeding in Early Liver Cirrhosis ............................................................................................................. 92
Youn Ju Jeon, Kyung Hoon Lee, Hyuk Soo Cho, Jung Hee Kwon, Kyung Min Sohn

PO-027  RIP3 Inhibition Promotes Steatosis in High Fat Diet Induced NAFLD ........................................................................................................... 92
Waqar Khalid Saeed, Dae Won Jun

PO-028  Prevalence of Vitamin D Deficiency in Chronic Liver Disease at the Outpatient Clinics of the University of the Philippines-Philippine General Hospital .................................................................................................................. 93
Aubrey Q. Taguba, Mariel Dianne S. Velasco, Mara Teresa T. Panfilo, Maria Joanne M. Rubio, Margaret Elaine J. Villamayor, Janus P. Ong, Ma. Lourdes O. Daez

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 .............................................................................................................. 93
In Suk Min, Ji Sang Shin, In Hee Kim, Chang Hun Lee, Se Young Seo, Seung Hun Kim, Sang Wook Kim, Seung Ok Lee, Soo Taek Lee, Dae Chon Kim

PO-030  Comparison of Long-term Efficacy of Tenofovir Monotherapy between Nucleos(t)ide-naive and Nucleos(t)ide-resistant Chronic Hepatitis B Patients ...................................................................................................................... 94
Young Min Shin, Kyung Hye Park, Seok Won Jung, Neung Hwa Park, Bo Ryung Park, Chang Jae Kim, Byung Uk Lee, Jae Ho Park, Byung Gu Kim, In Da Jeong, Sung-Jo Bang, Jung Woo Shin

PO-031  Obesity and Hepatocellular Carcinoma in Patients Receiving Entecavir for Chronic Hepatitis B .......................................................................... 94
Jaemin Lee, Sun Hong Yoo, Sang Park Jung, Young Min Park, Won Sohn

PO-032  The Effect of Tenofovir on Renal Function in Patients with Chronic Hepatitis B ................................................................................................. 94
Woo Jin Jung, Jae Young Jung, Seung Won Jeong, Se Hwan Lee, Sang Gyune Kim, Sang-Woo Cha, Young Seok Kim, Young Deok Cho, Hong Soo Kim, Boo Sung Kim, Su Yeon Park

PO-033  Clinical Course of Partial Virologic Responders under Prolonged Tenofovir Therapy in Nucleos(t)ide-naive Patients with Chronic Hepatitis B ......................... 95
Young Min Shin, Kyung Hye Park, Seok Won Jung, Neung Hwa Park, Bo Ryung Park, Chang Jae Kim, Byung Uk Lee, Jae Ho Park, Byung Gu Kim, In Da Jeong, Sung-Jo Bang, Jung Woo Shin

PO-034  Significant Genomic Variants Associated with Hepatitis B Surface Antigen Seroclearance in Korea ........................................................................ 95
Tae Hyung Kim, Soon Ho Lim, Yeon Seok Seo, Sun Young Yim, Seung Moon Park, Han Ah Lee, Sang Jung Park

HBV, Clinical

PO-035  Impact of Antiviral Therapy with Tenofovir or Entecavir on Renal Function in Patients with Hepatitis B Virus-related Cirrhosis .......................................... 96
Jhye Park, Kyu Sik Jung, Beom Kyung Kim, Seung Up Kim, Do Young Kim, Sang Hoon Ahn, Kiwang-Hyub Han, Jun Yong Park
PO-054 Integrative Transcriptome and Metabolome Analysis of Hepatic Cancer Stem Cells
Wonhee Hur, Jae Yong Ryu, Hyun Uk Kim, Jun Ho Lee, Eun Byul Lee, Sang Yup Lee, Seung Kew Yoon

PO-055 Differential Hepatocarcinogenic Potentials between KRAS Splicing Variants
Hyuk Moon, Sook In Chung, Simon W. Ro, Kwang-Hyub Han

HCC, Clinical

PO-056 Missing Cases in Diagnosis of HCC 2 cm or More Sizes
Hyuk Jin Moon, Sae Hwan Lee, Hong Soo Kim, Sang Gyune Kim, Young Seok Kim, Boo Sung Kim, So Young Jeong, Jae Young Jung

PO-057 Development of Risk Prediction Model for Hepatocellular Carcinoma Progression of Indeterminate Nodules in Hepatitis B Virus-related Cirrhotic Liver
Hyo Jung Cho, Jong-Dong Lee, Dae Yong Kang, Bohyun Kim, Jei Hee Lee, Jae Keun Kim, Sung Jae Shin, Kee Myoung Lee, Byung Moo Yoo, Kwang Jae Lee, Soon Sun Kim, Jae Yoon Cheong, Sun Won Cho

PO-058 Need for Subclassification of BCLC-C Stage Hepatocellular Carcinoma and Treatment Strategies
Jae Hyun Yoon, Chong Hwan Jun, Eunae Cho, Sung Bum Cho, Sung Kyu Choi

PO-059 Substaging of Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma by Tumor Size, Major Portal Vein Invasion, Distant Metastasis and Liver Function
Dongwon Lee, Hyung Joa Kim, Seong Kyu Na, Seo Young Kim, Sung Jun Suh, Jong Jin Hyun, Sung Woon Jang, Young Kuk Jung, Je Seul Koo, Ji Hoon Kim, Yeon Seok Seo, Jong Eun Yeo, Sun Woon Lee, Kwan Soo Byun, Soon Ho Um

PO-060 Sub-classification of Advanced Stage Hepatocellular Carcinoma based on a Real-life Cohort
Jeong-Ju Yo, Jeong-Hoon Lee, Young Chang, Eunhu Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwaen Yoon, Seoul Liver Group

PO-061 Effects of Endoscopic Variceal Ligation for the Esophageal Varix in Patients with Advanced Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis
Sun Seok Park, Joong-Won Park, Bo Hyun Kim, Sunhao Yoo, Byung-Ho Nam, Chang-Mir Kim

HCC, Clinical

PO-062 sarcopenia as a Predictor of Survival and an Objective Measure of Performance Status in Hepatocellular Carcinoma
Yeongjung Ha, Young Eun Cho, Yun Bin Lee, Mi Na Kim, Joo Ho Lee, Hana Park, Seong Guu Hwang, Kyu Sung Rim

PO-063 Prognostic Values of Inflammation and Immune-based Scores in Patients with Hepatocellular Carcinoma Who Undergo Transarterial Chemoembolization
Eun Ju Cho, Su Jong Yu, Joon Yeul Nam, Young Chang, Hyeji Cho, Seong Hee Kang, Young Youn Cho, Jeong-Hoon Lee, Yoon Jun Kim, Hye-Cheol Kim, Chung Yong Kim, Jung-Hwaen Yoon

PO-064 Plasma MicrRNA-21, 26a, and 29a as a Predictive Marker for Treatment Response Following Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma
Soon Sun Kim, Ji Sun Nam, Hye Jung Cho, Ji-Hyun Kim, Han Kyed Kim, Ga Ram Lee, Je Hwan Won, Jun Wook Kim, Sung Won Cho, Jae Yoon Cheong

PO-065 EpCAM as a Predictive Marker of Tumor Recurrence and Survival in Patients with Hepatocellular Carcinoma after Surgical Resection
Choo-ng Kyun Nah, Hye Jong Wang, Jung Hee Kwon, Hye Jung Cho, Soon Sun Kim, Bong Wan Kim, Sung Won Cho, Jae Yoon Cheong

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
Yong Kwon Kim, Min Young Baek, Jae Yong Jung, Soong Won Jeong, Sae Hwan Lee, Sang Guu Kim, Sung-Koo Cha, Young Seok Kim, Young Deok Cho, Hong Soo Kim, Boo Sung Kim

PO-067 Clinical Significance of the Peritumoral Decreased Uptake Area on Hepatobiliary Phase of Gadoxetic Acid-enhanced MRT in Hepatocellular Carcinoma
Seung Kuk Shin, Yun Soo Kim, Young Sup Shim, Jeong Hoon Choi, So Hyun Park, Dong Hae Jung, Oh Sang Kwon, Duck Joo Choi, Ji Hyun Kim

HCC, Clinical

PO-068 Double Time of Serum Tumor Marker in HCC Patients Predicts Recurrence after Curative Treatment
Ji Hye Je, Yang Jee Yoo, Young-Sun Lee, Sung Jun Suh, Young Kuk Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joa Kim, Jong Eun Yeon, Kwan Soo Byun

PO-069 Assessment of Risk for Recurrence of Hepatocellular Carcinoma: An Extended Surveillance Interval 1 Year after Curative Treatment
Minhyong Lee, Sohee Oh, Young Youn Cho, Jeong-Hoon Lee, So Jong Yu, Nam-In Jo, Kwang-Woong Lee, Jeong Min Lee, Jung-Hwan Yoon, Kyu-Suk Suh, Yoon Jun Kim

PO-070 Does Transarterial Chemoembolization prior to Surgical Resection Improve Clinical Outcomes in Resectable Hepatocellular Carcinoma?
Hye Ji Kim, Jung Hyun Kwon, Young Woon Kim, Soon Wook Nam, Jong-Yul Lee, Hyun Suk Jung, Yu Ri Shin, Young Chul Yoon, Jun Suk Lee, Sung Won Lee, Hae Lim Lee
PO-071 Prognosis of Early Stage Hepatocellular Carcinoma Showing Complete Response after First Transarterial Chemoembolization: A Role of Scheduled Second TACE .......................... 112
Jung Hee Kim, Dong Hyun Sihn, Sung Wook Shin, Sung Ki Cha, Wonsok Kang, Geum-Youn Gwaik, Joon Hyek Lee, Kwang Sool Koh, Seung Woon Paik, Moon Sook Choi

PO-072 Three-dimensional Conformal Radiotherapy for Portal Vein Tumor Thrombosis in Advanced Hepatocellular Carcinoma .......................... 113
Moon Won Lee, Hyun Young Woo, Jeong Hee, Won Lim, Young M. Hong, Ki Tae Yoon, Mong Cho, Won Taek Kim

PO-073 Radiation Induced Liver Disease after Stereotactic Body Radiation Therapy for Small Hepatocellular Carcinoma: Risk Factor and Clinical Significance .................................................. 113
Baek Gyu Jun, Young Don Kim, Gab Jin Cheon, Sae Hwan Lee, Hong Soo Kim, Sang Gyune Kim, Young Seok Kim, Boo Sung Kim, Seung Won Jeong, Jae Young Jang

HCC, Clinical

PO-074 Clinical Outcomes of Patients with a Single Hepatocellular Carcinoma Less Than 5 cm Treated with Transarterial Chemoembolization .................. 114
Min Yyoung Baek, Soong Won Jeong, Jae Young Jang, Sae Hwan Lee, Sang Gyume Kim, Sang-woo Cha, Young Seok Kim, Young Deok Cha, Hong Soo Kim, Boo Sung Kim

PO-075 Long Term Results of Combined Transarterial Chemoembolization with Radiofrequency Ablation in Hepatocellular Carcinoma of 2 to 5 cm in Diameter .................................................. 114
Mi-Young Kim, Dae-Seong Myung, Chung-Hwan Jun, Won-Sik Lee, Jin Woong Kim, Yang Jun Kang, Sung-Kyu Choi, Young-Eun Joo, Sung-Bum Cho

PO-076 Transarterial Infusion of Epirubicin and Cisplatin Combined with Systemic Infusion of S-FU for Advanced Hepatocellular Carcinoma Refractory to Conventional Transarterial Infusion with Doxorubicin .......................... 115
Young Woon Kim, Jung Hyun Kwon, Soon Woon Nam, Jung-yul Lee, Jeong Won Jang, Kyu Won Chung, Hyun Suk Jung, Yu Ri Shin

PO-077 Safety and Feasibility of Laparoscopic Major Hepatectomy (LVMH) Post Portal Vein Embolization (PVE), A Case Series .................................................. 115
Nasser Alzenei, Choon Hyuck David Kwon, Wontae Cho, Seung Hwan Lee, Jin Yong Choi, Jae-Won Joo

PO-078 Can Sorafenib Increase Survival for Recurrent Hepatocellular Carcinoma after Liver Transplantation? .................................................. 115
Seong Hee Kang, Eun Ju Cho, Jooyeon Nam, Young Chang, Hyekki Cho, Young Youn Jeong, Hyun-Hoon Lee, Su Jong Yu, Yoon Jun Kim, Nam-Joon Yi, Kwang-Woong Lee, Kyung-Suk Suh, Jung-Hwan Yoon

HCC, Clinical

PO-079 An Analysis for Survival Predictors for Patients with Hepatocellular Carcinoma Who Failed to Sorafenib Treatment .......................... 116
Young-Sun Lee, Ji Hoon Kim, Yang Iae Yoo, Ihye Je, Sang Jun Suh, Young Kul Jung, Yeon Seok Seo, Hyung Joan Yim, Joon Eun Yeon, Kwan Soo Byun

PO-080 Oral Medications Improve Overall Survival by Enhancing Adherence to Regular Surveillance for Hepatocellular Carcinoma: Results of Mediation Analysis ............................................................................. 116
Jooyeon Nam, Jeong-Hoon Lee, Jeun E Kim, Dong Hyon Lee, Young Chang, Hongkeun Ahn, Hyekki Cho, Jung-su Yoo, Minjong Lee, Young Youn Cho, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon

PO-081 Comparison of Prognostic Staging Systems for Hepatocellular Carcinoma in a Hepatitis B Virus Endemic Area .......................... 117
Bo Hyun Kim, Boram Park, Jungnam Joo, Joong-Won Park, Chang-Min Kim

PO-082 Role of Endoscopic Biliary Drainage in Advanced Hepatocellular Carcinoma with Jaundice .......................... 118
Hyun Young Woo, Sung Yong Han, Jeong Heo, Dong Uk Kim, Dong Hoon Baek, Won Lim, Ki Tae Yoon, Young Mi Hong, Mong Cho

PO-083 Albumin-bilirubin Grade and Long-term Survival in Very Early Stage Hepatocellular Carcinoma who Received Either Resection or Ablation .... 118
In Soo Oh, Dong Hyun Sihn, Ji Hyeon Lee, Jung Hee Kim, Wonsok Kang, Geum-Youn Gwaik, Yong-Ho Park, Moon Seok Choi, Joon Hyek Lee, Kwang Sool Koh, Seung Woon Paik

PO-084 Clinical Outcomes of Intraoperative Radiofrequency Ablation in Hepatocellular Carcinoma Patients Ineligible for Percutaneous Radiofrequency Ablation or Surgical Resection .................................................. 118
Sung Woon Lee, Hae Lim Lee, Jung Hyun Kwon, Jun-Suh Lee, Young Chul Yoon, Yu Ri Shin, Hyee Ji Kim, Eun Chung, Young Woon Kim, Jeong Won Jang, Soon Woon Nam, Nam Ik Han, Kyu Won Chung

Surgery

PO-085 Outcomes of Living and Deceased Donor Liver Transplant Recipients according to the MELD Score .......................... 119
Jae Geun Lee, Jihan Lee, Jung Jun Lee, Seung Hwan Song, Jeeyoon Yoon, Se-kyung Kwon, Dong Jin Joo, Min Ki Ju, Gi Hong Choi, Joon Sub Choi, Soon Il Kim, Myoung Soo Kim

PO-086 Transplantation versus Hepatectomy for Hepatocellular Carcinoma 2 cm or Less Than 2 cm .................................................. 120
Xu-Guang Hu, Hee-Jung Wang, Bing-Wan Kim, Mao Wei, Sung Yeon Hong

PO-087 HSV after LDLT .................................................. 120
Abytakhan Sharmanov, Gani Kutsyrmuratov, Tokan Sultnaliyev, Mukhanov Adilbek, Zhoksembayev Asan, Yermahan Assylkanuly, Meli Askdybayev, Said Abdugafarov
PO-088  LDLT for Non-cirrhotic Portal Hypertension from Cavernous Transformation of Portal Vein - A Case Report  .................................................. 120
Sung Yeon Hong, In-Gyu Kim, Xu-Guang Hu, Hee-Jung Wang, Bong-Wan Kim

PO-089  Changes in T Cells in Peripheral Blood after Adult Liver Transplantation .............................................................. 121
Jong-Man Kim, Jisoo Lee, Kyung-Sik Kim, Nuri Lee, Chan-Woo Cho, Gyu-Seong Cho, Choonthyuck David Kwon, Jae-Won Ioh

Surgery

PO-090  Relevance of the Tumor Site and Node Metastasis in Patients with Intrahepatic Cholangiocarcinoma ............................................................... 121
WooHyung Lee, Jae Yool Jang, Soon-Chan Hong, Chi-Young Jeong

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) .................................................. 122
In-Gyu Kim, Xu-Guang Hu, Hee-Jung Wang, Bong-Wan Kim, Sung Yeon Hong

PO-092  Case-control Study of Pure Laparoscopic Hemiepatectomy vs. Open Left Hemiepatectomy for Hepatocellular Carcinoma .................................................. 122
Hwa-Dong Cho, Ki-Hun Kim, Shin Hwang, Chul-Soo Ahn, Duk-Bok Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park, Sung-Gyu Lee

PO-093  The Role of Curative Intent Surgical Resection for the Recurrent HCC ................................................................. 122
Seung Hwan Song, Jee Youn Lee, Suk-Jin Jang, Chi-Young Jeong

Poster Exhibition

1. Alcoholic Liver Disease

PE-001  Outcome of Deceased Donor Liver Transplantation for Alcoholic Liver Disease .................................................. 127
Suk Kyun Hong, Nam-Joon Yi, Kyung Chul Yoon, Hyo-Sin Kim, Hyeyoung Kim, Kwang-Woong Lee, Kyung-Suk Suh

PE-002  Liver Transplantation for Alcoholic Liver Disease ................................................................. 127
Yermakhan Assylkhanuly, Gani Kuttymuratov, Bakhyt Zharkimbekov, Mels Asykbayev, Saitkarim Abdugafarov

PE-003  Predictive Factors of Death or Transplantation in Patients with Severe Alcoholic Hepatitis Treated with Prednisolone .................................................. 127
Young Seok Do, Seong Kyo Na, Eui Ju Park, Gang Mo Kim

PE-004  The Frequency of Peripheral CD1d+ NKT Cell Can Be Biomarker for Steroid Therapy in Patients with Severe Alcoholic Hepatitis .................................................. 128
Ji Young Kim, Chang Wook Kim, Yun Hui Kim, Seok Cheon Yeom, Su Gyeong Lee, Hee Yeon Kim, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon

2. Cell Biology / Molecular Biology

PE-005  Genetic Alterations of the SIAH-1 Gene in Hepatocellular Carcinomas ................................................................. 128
Neung Hwa Park, Chang Jae Kim, Jung Woo Shin, Seok Won Jung, Bo Ryung Park

PE-006  Inactivating Mechanism of ATBF1 Gene in Hepatocellular Carcinomas .................................................. 128
Neung Hwa Park, Chang Jae Kim, Jung Woo Shin, Seok Won Jung, Bo Ryung Park

PE-007  WT1 Is the Regulatory Gene in the Process of Hepatocyte-like Cells Differentiation from Bone Marrow Mesenchymal Stem Cells .................................................. 129
Jung Hoon Cha, Na Ri Park, Ho-Shik Kim, Jong Young Choi, Seung Kew Yoon, Si Hyun Bae

PE-008  Calcium Mobilization through L-type Channels in Hepatic Stellate Cell Is Essential for TGF-b-mediated CTGF .................................................. 129
Jonghwa Kim, Soo Hee Kang, Sook Hyun Park, Ju-yeon Cho, Won Sahn, David A. Brenner, Yong-Han Park

PE-009  3D Printing of Mouse Primary Hepatocytes for Generating 3D Hepatic Structure .................................................. 129
Sungho Jang, Kyojin Kang, Hyereon Jeon, Jaemin Jeong, Su A Park, Wan Doo Kim, Seung Sam Park, Dongho Choi

3. Drug and Toxic Injury

PE-010  ZLITHAMACR ................................................................. 130
Byung Seok Lee, Seok Hyun Kim, Eun Soo Leek, Ju Seok Kim, Jong Seok Joa, Hae Jin Shin, Hyuk Soo Eun, Woo Sub Kim

4. Genetic

PE-011  The Major Changes of Gilbert’s Syndrome and UGT1A1 Gene Abnormalities in Mongolians Are Western Type .................................................. 131
Nyam Biza, Nyamaa Bayarmaa, Ju-Ting Hu, May-Jen Huang, Ching-Shian Huang, Si-en Ting Yang
Contents

PE-012  Genes Associated with Prognosis of Hepatocellular Carcinoma: Validation of Microarray Results Using Quantitative Real Time RT-PCR ............................... 131
    Jung-Hee Kwon, Keun Soo Ahn, Yun Suk Yu, Jin Young Park, Gundo Kim, Seung Whan Kim, Hong Du Gu, Hee Jung Wang, Jae Won Jh, Koo Jeong Kang

PE-013  Severe Indirect Hyperbilirubinemia Patient with NT-211G>A Variant of UGT1A1 Gene ................................................................. 132
    Baterden Dashiyan, Narash Uyang, Monkhabatar Tsardsuren, Erdertiya Derem, Gantuya Baigan, Nyam Boia

PE-014  Liver Involvement in Sickle Cell Trait: A Case Control Study among Nepalese Indigenous Tharu Community ......................................................... 132
    Bhop Dev Bhatta, Mukund Kalouni, Amrit Bhandari, Sunita Ranabhat

PE-015  The Association between Tumor Necrosis Factor-alpha Polymorphism (-308, G/A) and Acute Solid Organ Rejection ...................................................... 132
    Min-Su Park

PE-016  Whole-genome Sequencing of Two Liver Tumors from One Patient ................................................................. 133
    Tae Hyung Kim, Soon Ho Um, Yeon Seok Seo, Seung Woon Park, Han Ah Lee, Sang Jung Park, Dong-Sik Kim, Young Dong Yu, Sung Won Jung, Jae Hyun Han, Joo Young Kim

5. HBV, Basic

PE-017  Suppression of Interferon-mediated Anti-HBV Response by a Single CpG Methylation in 5’UTR of TRIM22 .............................................................. 133
    Eun-Sook Park, Doo Hyun Kim, Ah Ram Lee, Soee Park, Heewoo Sim, Juhee Won, Kyun-Hwan Kim

PE-018  Hepatitis B Virus Enhances Promoter Activity of Alpha-fetoprotein in Cytokine-dependent Manner .............................................................. 133
    Jae Hee Choi, In Young Moon, Jung Wha Chung, Jinwood Kim

PE-019  Marked Decreases of Foxp3 and CTLA-4 Are Associated with Strong Antiviral Effects of Tenofovir in Patients with Chronic Hepatitis B ..................... 134
    Ji Young Kim, Chang Wook Kim, Yun Hai Kim, Seok Cheon Yeom, Su Gyeong Lee, Hee Yeon Kim, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon

PE-020  Foxp3 and PD-1 Except CTLA-4 Are Decreased Significantly during 1 Year Tenofovir Therapy in Chronic Hepatitis B ........................................ 134
    Hyeoun Cho, Chang Wook Kim, Ji Young Kim, Yun Hui Kim, Seok Cheon Yeom, Su Gyeong Lee, Hee Yeon Kim, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon

6. HBV, Clinical

PE-021  Clinical and Virological Features in Chronic Hepatitis B Patients with Entecavir Resistance .......................................................... 134
    Myung Jin Oh

PE-022  HBsAg Level Change in Chronic Hepatitis B Patients Who Achieved Virological Response with Oral Antiviral Agents .............................................. 135
    Won Hyeok Choe, So Young Kwon, Byung-chul Yoo, Jeong Han Kim

PE-023  Clinical, Biochemical and Virological Differentiation in Acute Hepatitis B and Chronic Hepatitis B with Acute Exacerbation ................................... 135
    Myung Jin Oh

PE-024  Treatment Modification Is not Needed for Early Alanine Aminotransferase Flare in Treatment-naive Patients with Chronic Hepatitis B Initiated on Tenofovir ........................................................ 136
    Jong Gu Lim, Jin Yong Kim, Jeong-Rok Lee, Joan Ho Wang, Jeong Han Kim, Won Hyeok Choe, So Young Kwon, Soon Young Ko

PE-025  Insulin Resistance Increases Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients .......................................................... 136
    Jung Hee Kim, Dong Hyun Sinn, Geum-Yoon Gwak, Wonseok Kang, Yong-Han Park, Moon Seok Choi, Soon Hyeok Lee, Kwang Cheol Kih, Seung Woon Park

PE-026  Histological and Clinical Features of Chronic Hepatitis B Patients with Persistent Viral Load and Normal or Slightly Elevated Serum Alanine Aminotransferase Levels .................................................................................. 136
    Dong Hee Shin, Jong-Won Park, Bo Hyun Kim, Chang-Min Kim, Eun Kyung Hong

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 ................................................................. 137
    Young Min Shin, Kyungs Hye Park, Seok Won Jung, Neung Hwa Park, Bo-Ryung Park, Chang Jae Kim, Byung Uk Lee, Jae Ho Park, Byung Giu Kim, In Do Jeong, Sung-Io Bang, Jung Wook Shin

PE-028  Comparison of Efficacy between Tenofovir Disoproxil Fumarate and Entecavir in Chronic Hepatitis B Patients with High Hepatitis B Virus DNA ........................ 137
    Hyocho Cho, Hongikun Ahn, Yoon Jun Kim, Young Chang, Joan Yeo Nam, Young Young Cho, Seong Hee Kang, Eun Ju Cho, Jeong-Hoon Lee, Su Jung Yu, Jung-Hwan Yoon

PE-029  Prolonged Tenofovir Monootherapy for Partial Virologic Response to Tenofovir in Treatment-naive Chronic Hepatitis B Patients ................................. 138
    Min Keun Kim, Sanghe Baek, Ga Young Kim, Hyochoon Chul Lee, Hyesun Lee, Eun Seong Jeong, Byung Seok Kim

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 .......................................................... 138
    Sun Young Shin, Joo Ho Lee

PE-031  Development of Hepatocellular Carcinoma after Hepatitis B Surface Antigen Seroclearance in Chronic Hepatitis B ........................................ 139
    Sun Hong Yoo, Won Sohn, Sang Jong Park, Young Min Park

www.theliverweek.org xxvii
### The Liver Week 2016

#### PE-037 Efficacy of Ledipasvir/Sofosbuvir plus Ribavirin among Patients with Decompensated Cirrhosis Who Underwent Liver Transplant during Participation in the SOLAR-1/-2 Studies

Beate Müllerhaup, Paul Kwo, Kosh Agarwal, Christophe Duval, Francois Durand, Marcus Peck-Radosavljevic, Eric M. Yoshida, Leslie Lilly, Bernard Willems, Hugo Vargas, Princy Kumar, Robert S. Brown, Yves Homans, Shampa De-Oertel, Sarah Arterburn, Hadas Devon-Sobol, Diana M. Brainard, John G. Mutchison, John Woo Bocko, Norah Torres, Marco Rizzetto

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**Page:** 141

**Authors:** Beate Müllerhaup, Paul Kwo, Kosh Agarwal, Christophe Duval, Francois Durand, Marcus Peck-Radosavljevic, Eric M. Yoshida, Leslie Lilly, Bernard Willems, Hugo Vargas, Princy Kumar, Robert S. Brown, Yves Homans, Shampa De-Oertel, Sarah Arterburn, Hadas Devon-Sobol, Diana M. Brainard, John G. Mutchison, John Woo Bocko, Norah Torres, Marco Rizzetto

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#### PE-040 False Positive Rates of Conventional Screening Test for Hepatitis C Virus Infection in Low Prevalent Area

Hyung Su Kim, Ji Won Kang, Sung Eun Kim, Sang Eun Kim, Su Bin Shin, Myoung Kuk Jang, Sang Hoon Park, Dong Jo Kim, Myung Seok Lee, Choong Kee Park

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**Page:** 143

**Authors:** Hyung Su Kim, Ji Won Kang, Sung Eun Kim, Sang Eun Kim, Su Bin Shin, Myoung Kuk Jang, Sang Hoon Park, Dong Jo Kim, Myung Seok Lee, Choong Kee Park

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---

#### PE-041 Long-term Follow-up of Patients with Chronic HCV Following Treatment with DAAs: Maintenance of SVR, Persistence of Resistance and Clinical Outcomes

W. Ray Kim, Erica C. Lavitz, Peter Raeue, Catherine Stedman, Graham Foster, Robert H. Hyland, Sarah Coogan, Stephanie Moody, Hadas Devon-Sobol, Steven J. Knox, Diana M. Brainard, Sunil Hwang, Armand Abergel, Kosh Agarwal, Ziad Younes, Christian Schwabe

**Session:** Clinical

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**Authors:** W. Ray Kim, Erica C. Lavitz, Peter Raeue, Catherine Stedman, Graham Foster, Robert H. Hyland, Sarah Coogan, Stephanie Moody, Hadas Devon-Sobol, Steven J. Knox, Diana M. Brainard, Sunil Hwang, Armand Abergel, Kosh Agarwal, Ziad Younes, Christian Schwabe

**Institution:**

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**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-042 Epidemiology and Genotype Distribution of HCV in Mongolia

Sooribam Anunaa, D. Munkh-Ochirikh, Ch. Bolormaa, B. Gansaghan, O. Bairarkhoo

**Session:** Clinical

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**Authors:** Sooribam Anunaa, D. Munkh-Ochirikh, Ch. Bolormaa, B. Gansaghan, O. Bairarkhoo

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**Country:**

**Keywords:**

**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-043 Treatment Outcomes on Chronic Hepatitis C Virus in Mongolia

S. Munkhjambal, S. Anunuu, L. Undsamb, O. Bairarkhoo

**Session:** Clinical

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**Page:** 144

**Authors:** S. Munkhjambal, S. Anunuu, L. Undsamb, O. Bairarkhoo

**Institution:**

**Country:**

**Keywords:**

**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-044 The Efficacy and Safety of Daclatasvir and Asunaprevir for Hepatitis C Virus Genotype 1 Infection in Old Age Patients with Compensated Cirrhosis

Hee Chul Nam, Hyun Yang, Hee Lim Lee, Myeong Jun Song

**Session:** Clinical

**Abstract ID:** PE-044

**Page:** 145

**Authors:** Hee Chul Nam, Hyun Yang, Hee Lim Lee, Myeong Jun Song

**Institution:**

**Country:**

**Keywords:**

**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-045 Clinical Adherence to KAS Guidelines for the Management of Adverse Events in Treating Chronic Hepatitis C with Interferon Based Regimen

Hana Park, Ji Yeon Kim, Tae Yeob Kim, Nae-Yun Heo

**Session:** Clinical

**Abstract ID:** PE-045

**Page:** 145

**Authors:** Hana Park, Ji Yeon Kim, Tae Yeob Kim, Nae-Yun Heo

**Institution:**

**Country:**

**Keywords:**

**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-046 Nationwide Seroprevalence of Hepatitis C Virus Infection in South Korea, Data from National Health and Nutrition Examination Survey 2012–2014

Kyung-Ah Kim, June Jung Lee, Moon Ki, Sook-Hyang Jeong

**Session:** Clinical

**Abstract ID:** PE-046

**Page:** 145

**Authors:** Kyung-Ah Kim, June Jung Lee, Moon Ki, Sook-Hyang Jeong

**Institution:**

**Country:**

**Keywords:**

**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-047 Efficacy and Safety of Ombitasvir, Paritaprevir/Ritonavir, and Dasabuvir without Ribavirin in Patients with HCV Genotype 1b: Pooled Analysis

Wenzel TM, Jankow V, Ting R, Streu-Cereca A, Dufour F-J, Marinho RT, Moreno C, Lu L, Xie W, Tatsch F, Shulman NS, Cravi A

**Session:** Clinical

**Abstract ID:** PE-047

**Page:** 146

**Authors:** Wenzel TM, Jankow V, Ting R, Streu-Cereca A, Dufour F-J, Marinho RT, Moreno C, Lu L, Xie W, Tatsch F, Shulman NS, Cravi A

**Institution:**

**Country:**

**Keywords:**

**Background:**

**Objective:**

**Results:**

**Conclusion:**

---

#### PE-049 Analysis of Hepatitis C Virus NS3 and NS5A Resistance Mutations after Daclatasvir plus Asunaprevir Treatment Failures in Korea

Seungtaek Kim, Hye-Jung Park, Hye Won Lee, Kwang-Hyub Han, Sang Hoon Ahn

**Session:** Clinical

**Abstract ID:** PE-049

**Page:** 147

**Authors:** Seungtaek Kim, Hye-Jung Park, Hye Won Lee, Kwang-Hyub Han, Sang Hoon Ahn

**Institution:**

**Country:**

**Keywords:**
### 8. Liver Cancer, Basic

**PE-054** Association of MicroRNA Machinery Genes with Hepatocellular Carcinoma in a Korean Population

M Ji Na Kim, Nam Kwon Kim, Seung Min Lee, Jung Oh Kim, Hana Park, Ju Ho Lee, Kyo Sung Rim, Seong Gyu Hwang

**PE-055** Differential Tumorigenic Effects by C-Myc Mutants in Liver Cancer

Daeyoung Kim, Hyuk Moon, Sooik Jhung, Simon Wh Po, Kwang Hyub Han

**PE-056** Changes in Immunologic Function after Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

Hana Park, Jie Ye Song, Hae Jung An, Yoon Bin Lee, Ju Ho Lee, Mi Na Kim, Young Eun Chun, Yeon Jung Ha, Seong Gyu Hwang, Kyo Sung Rim

**PE-057** First Experience of Using Two-stage Resection of the Liver (Split in situ) in Patients with Metastatic Colorectal Cancer

Zhanat Spatayev, Asein Zheymbayev, Adilek Mukazhanov, Baurzhan Brayev, Aymkul Ashikhanova

**PE-058** Roles of SS18L1 Polymorphisms in Predicting Prognosis of Hepatocellular Carcinoma

Min Su Park

**PE-059** Downregulation of Raf-1 Kinase Inhibitory Protein as a Sorafenib Resistance Mechanism in Hepatocellular Carcinoma Cell Lines

Jin Sun Kim, Yu Sun Jung, Kang Mo Kim, Se Jin Jang, Han Chu Lee

### 9. 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

Min Jung Jun, Ju Hyun Shim, Joo Ho Lee, Gi Won Song, Yangsoo Park, Eunsil Yu, Sung Gyu Lee, Ji Hyun An, Danbi Lee, Kang Mo Kim, Young Suk Lim, Han Chu Lee, Young Hwa Chung, Yang Sang Lee

**PE-061** Living Donor Liver Transplantation for Giant Hepatic Hemangioma with Diffuse Hemangiomatisis in an Adult: A Case Report

Ji Hyun Lee, Sang Hyuk Im, Boom Hee Kim, Chung Seop Lee, Jung Wha Chung, Chang Jin Yoon, Young Hoon Kim, Jia Young Cho, Haeyoung Kim, Eun Sun Jang, Jin Wook Kim, Sook Hyung Jeong

**PE-062** The Clinical Implication of Anatomical Liver Resection in Patients with Hepatocellular Carcinoma in Aspect of Stemness Marker CD 133 Expression

Moo Hyun Kim, Yoo Li Lim, Sung Hoon Kim, Mee Yeon Cho, Moon Young Kim, Soon Koo Baik

**PE-063** Incidence of Hepatocellular Carcinoma in Subjects with Hepatitis B Virus Positive in Korean National Liver Cancer Screening Program

Jae Jun Shim, Tae Woong Cho, Chi Hyuck Oh, Soyoung Park, Yu Jin Um, Byung Ho Kim

**PE-064** Risk of Hepatocellular Carcinoma Development Is Much Higher in Korean Patients with Chronic Hepatitis B than in Taiwanese

Jae Jun Shim, Tae Woong Cho, Chi Hyuck Oh, Soyoung Park, Yu Jin Um, Byung Ho Kim

**PE-065** Application of REACH-B Model to Predict Hepatocellular Carcinoma Risk in Patients with Chronic Hepatitis B under Oral Antiviral Therapy

Jae Jun Shim, Tae Woong Cho, Chi Hyuck Oh, Soyoung Park, Yu Jin Um, Byung Ho Kim

**PE-066** Obesity and the Risk of Mortality in Newly-diagnosed Hepatocellular Carcinoma

Jung Hee Kim, Dong Hyeon Sim, Geum Young Gwak, Wonseok Kang, Yong Han Paik, Moon Seok Cho, Joon Hyeok Lee, Kwang Cheol Koh, Seung Woon Paik

**PE-067** Primary Prophylaxis for Variceal Bleeding Improves Survival of Patients with Newly-diagnosed Hepatocellular Carcinoma

Jung Hee Kim, Kyung Ha Kim, Ki Yeon Kim, Wonseok Kang, Geum Young Gwak, Yong Han Paik, Moon Seok Cho, Joon Hyeok Lee, Kwang Cheol Koh, Seung Woon Paik, Dong Hyeon Sim

**PE-068** Clinical Profile, Prognostic Factors, and Survival of Patients with Hepatocellular Carcinoma in Two Philippine Tertiary Centers

Mara Teresa T. Panlilio, Rei Joseph P. Pieter, Angela D. Djajakusuma, Neil S. Bacaltos, Cynthia A. Balagot, Jade B. Jamias, Ramon L. de Vera, Janus P. Ong
PE-069 Therapeutic Priority for a Solitary Large Hepatocellular Carcinoma in South Korea: An Analysis of Nationwide Cancer Registry Database
Young-Ioo Jin, Jin-Woo Lee

PE-070 Epidemiology and Prognosis of Hepatocellular Carcinoma in Mongolia
Dashchirev Munkh-Odshikh, S.Khurem, J.Chinburen, M.Sagarsuren, J.Amarsanaa, ODIY-BIAATMRKHU

PE-071 The Possibility of Radiotherapy for Downstaging before Living Donor Liver Transplantation for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis
Jin Yong Cho, Jong Min Kim, Choon Hyuck David Kwon, Jae-Won Joh, Gyu-Seong Choi

PE-072 Macrovascular Invasion of Hepatocellular Carcinoma Is not an Absolute Contraindication for Living Donor Liver Transplantation
Kwang-Woong Lee, Suk-Won Suh, Jeahong Jeong, Hyeyoung Kim, Nam-Joon Yi, Kyung-Suk Suh

PE-073 Minimal Incision Right Donor Hepatectomy: A Single Center Experience
Adianto Nugroho, Hyeyoung Kim, Nam-Joon Yi, Kwang-Woong Lee, Kyung-Suk Suh

PE-074 Validation of the MORE Score Model Predicting Survival of Patients with Recurrent or Progressive Hepatocellular Carcinoma
Sang Il Choi, Joong-Won Park, Bo Hyun Kim, Yoosun Choi, Byung-Ho Nam

PE-075 Colonoscopic Cyanoacrylate Injection of Bleeding Ileal Varices in a Patient with Hepatocellular Carcinoma
Arend Bernice G. Timbol, Eric B. Yasay, Mark Anthony A. De Luzong

PE-076 Detection of Hepatocellular Carcinoma at Advanced Stages in Patients with Chronic Hepatitis B Who Underwent Regular Surveillance: Predictors for Detection Failure
Young Eun Chon, Kyu Sik Jung, Jun Yong Park, Sang Hoon Ahn, Beom Kyung Kim, Seung Up Kim, Hana Park, Seong Kyeu Hwang, Kyu Sung Kim, Kwang-Hyub Han, Do Young Kim

PE-077 The Association between the State of Lipiodol Uptake after TACE and Recurrence of HCC
Soo Yeon Jo, Soo Hyung Ryu, Jung Hwa Min, Kyung Jin Lee, Bo Kyung Kim, Won Jae Yoon, Jeong Seop Moon

PE-078 Influence of Alcohol Intake on the Stage and Outcomes of Hepatocellular Carcinoma
Ji Hee Park, Joong-Won Park, Bo Hyun Kim, Sunhoon Yoo, Byung Ho Nam, Chang-Min Kim

PE-079 A Case of Primary Angiosarcoma with Diffuse Hepatic Involvement
Seok Chun Yeum, Chang Wook Kim, Hee Yeon Kim, Sukyoung Lee, Yoo Dong Won, Se Lim Lee

PE-080 Development of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B under Oral Antiviral Therapy
Jae-Jun Shim, Tae-Woong Choi, Chi Hyuck Oh, Sooyung Park, Yu Jin Um, Byung-Ho Kim

PE-081 The Clinical Outcomes of Advanced HCC Patients Received Systemic Cytotoxic Chemotherapy after Sorafenib Failure
Young-Sun Lee, Ji Hoon Kim, Yang Jae Yoo, Jiye Je, Sang Jun Suh, Young Kuk Jung, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon, Kiwan Sae Byun

PE-082 Prediction of Response to Sorafenib in Hepatocellular Carcinoma: A Marker Panel by Multiple Reaction Monitoring-mass Spectrometry
Hyunsoo Kim, Se Jung Yu, Injun Yeo, Jeong-Ju Yoo, Dong Hyeon Lee, Yuni Cho, Eun Ju Cho, Jeong-Ho Ha, Yoon Jin Kim, Sungyoung Lee, Jungsoo Jun, Taesung Park, Jung-Hwan Yoon, Youngsoo Kim

PE-083 Impact of Pretreatment Contrast Enhancement Features on Radiotherapy Outcome in Hepatocellular Carcinoma
Sang Min Yoon, Nuri Hyun Jung, So Yeon Kim, Jin-ho Park, Sang-won Lee, Jong Hoon Kim

PE-084 Two Cases of Intraductal Papillary Neoplasm of the Bile Duct with Associated Invasive Carcinoma
Ho Jong Choi, Il Young Park

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
Wang Yong Cho, Woo In Chung, S.Hyun Bae, Do Seon Song, Myeong Jun Song, Young Seok Kim, Hyung Joong Kim, Yong Kuk Jung, Sang Jun Suh, Jun Yong Park, Do Young Kim, Seung Up Kim, Sung Bum Cho

PE-086 Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Huge Hepatocellular Carcinoma Combined with Liver Cirrhosis and Portal Hypertension
Hyung-Jae Park, Tae Wan Lim, Sae Byeoil Choi, Won Bae Kim, Sang Yang Choi

PE-087 Treatment Outcome and Prognosis of Patients with Hepatocellular Carcinoma with Inferior Vena Cava and/or Cardiac Invasion
Seawon Hwang, Bo Hyun Jung, Pil Soo Sung, Jeong Won Jung, S.Hyun Bae, Jong Young Choi, Seung Kew Yoon

PE-088 Sarcopenia May Be Associated with the Mortality in Patients with Hepatocellular Carcinoma
Sung Eun Kim, Ji Won Park, Hyunsoo Kim, Ki Tae Suk, Myung Kuk Jung, Sang Hoon Park, Myung Seok Lee, Dong Joon Kim, Choong Koo Park

PE-089 Totally Intra-corporeal Laparoscopic Liver Resection for Rt. Posterior Segment by Extracorporeal Glissonean Approach with Hanging-over Maneuver
Sam-Youl Yoon, Hyung-Jun Han, Yun-Sang Go, Tae-Ink Song
Contents

PE-090  Staged Partial Hepatectomy versus Transarterial Chemoembolization for the Treatment of Spontaneous Hepatocellular Carcinoma Rupture : A Multicenter Analysis in Korea .............................................................. 165
Hyung Soon Lee, Gi Hong Choi, Jin Sub Choi, Kwang-Hyub Han, Sang Hoon Ahn, Do Young Kim, Jun Yong Park, Seung Up Kim, Sung Hoon Kim, Yoon Dang Sup, Jae Keun Kim, Jong Won Choi, Soon Sun Kim, Hana Park

PE-091  Prognostic Factors after Resection for Large Hepatocellular Carcinoma Over 5 cm ............................................................ 165
ji Hyun Noh, Tae-Seok Kim, Keun Soo Ahn, Yong Heon Kim, Koo Jeong Kang

PE-092  Pathologic Response to Preoperative Transarterial Chemoembolization for Resectable Hepatocellular Carcinoma May Not Predict Recurrence after Liver Resection .............................................................. 165
Kwang Yeol Paik, Eung Kook Kim

PE-093  Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Huge Hepatocellular Carcinoma Combined with Liver Cirrhosis and Portal Hypertension .............................................................. 166
Young-Jae Park, Tae Won Lim, Sae Byeol Choi, Wan Bae Kim, Sang Yong Choi

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 .............................................................. 166
Young Yeon Cho, Young Seok Han, Heon Taik Ha, Hyung Jun Kwon, Jae Min Chun, Sang Geol Kim, Yoon Jin Hwang

PE-095  The Treatment Strategy of Hepatocellular Carcinoma Planned Hepatic Resection in Accordance with BCLC Staging Classification : Is It Golden Rule? .............................................................. 167
Young Mok Park, Tae Beom Lee, Byung Hyun Choi, Kwang Ho Yang, Je Ho Ryu, Chong Wook Chu

10. Liver Cirrhosis, Portal Hypertension with Cx. Basic

PE-096  An Increased Incidence of Hepatocellular Cirrhosis in Fibrotic Livers .............................................................. 167
Kyungsoo Cho, Sook in Chung, Hyouk Moon, Simon W. Ro, Kwang-Hyub Han

PE-097  Comparisons of Non Invasive Parameters on Fibrosis Regression in Chronic Hepatitis B Patients on Entecavir Therapy .............................................................. 168
Gabriel Valero, Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Do Young Kim, Sang Hoon Ahn, Kwang Hyub Han, Jun Yong Park

PE-098  Effect of Rifaximin on the Hepatic Fibrosis in Bile Duct Ligated-rat Model .............................................................. 168
Seung Kuk Shin, Oh Sang Kwon, Jong Joon Lee, Duck Joa Choi, Yun Soo Kim, Ju Hyun Kim

PE-099  Post-resection Prognosis of Combined Hepatocellular Carcinoma-Cholangiocarcinoma according to the 2010 WHO Classification .............................................................. 168
Shin Hwang, Young-Joo Lee, Ki-Hun Kim, Chul-Soo Ahn, Desh-Bag Moon, Tae-Yong Ha, Seung-Mo Hong, Eun Sil Yu, Sung-Gyu Lee

11. Liver Cirrhosis, Portal Hypertension with Cx. Clinical

PE-100  Pyelolphlebitis Following Cyanoacrylate Injection into Duodenal Varix : A Rare Adverse Event .............................................................. 169
Eunae Cho, Chung Hwan Jun, Kyeon Man Cho

PE-101  Diagnostic Accuracy of Magnetic Resonance Elastography with Liver Fibrosis Assessment in Chronic Viral Hepatitis Patients .............................................................. 169
Hana Park, Dae Kyu Shin, Sun Young Shin, Suk Pyo Shin, Yun Bin Lee, Joo Ho Lee, Seong Gu Hwang, Kyu Sung Kim

PE-102  Treatment of End-stage Liver Disease in the JSC National Scientific Center for Oncology and Transplantology, Astana, Kazakhstan: Views and Perspectives .............................................................. 169
Kulpash Kaliaskarova, Yuriy Prokopenko, Zhansaya Muratova, Sergey Borovskiy, Tokan Sultanalyev, Adilbek Mukachanov, Bakhyt Zharkimbekov, Assan Zhexembayev, Gani Kutymuratov, Bakhtiyar Amanzholov, Kakharman Yesmembetov

PE-103  Risk Factors for Initial Treatment Failure and Short-term Mortality of Spontaneous Bacterial Peritonitis in Patients with Liver Cirrhosis .............................................................. 170
Seung Bum Kim, In Hee Kim, Chang Hun Lee, Seung Young Sop, Seong Hun Kim, Sang Wook Kim, Seung Ok Lee, Soo Teik Lee, Dae Ghan Kim

PE-104  The Study for the Relation between Cardiac Diastolic Dysfunction and Prognosis in Patients with Decompensated Liver Cirrhosis .............................................................. 170
Seok Hwan Kim, Hye Jun Ahn, Ji Chang Kim, Myeong Jun Song

PE-105  The Safety and Efficacy of Plug-assisted Retrograde Transvenous Obliteration for the Treatment of Gastric Varices: Single Tertiary Hospital Experience .............................................................. 171
Young Mi Hong, Seung Bum Lee, Ki Tae Yoon, Mong Cho, Ung Bae Jeon, Won Lim, Hyun Young Woo, Jeong Heo

PE-106  Presence of Anemia Predicts Advanced Grade at Presentation in Patients with Hepatic Encephalopathy .............................................................. 171
Nauman Arif Jadoon, Zeeshan Butt, Ahmed Shahzad, Kamran Musthak

PE-107  Hyponatremia in Decompensated Cirrhosis: Is It Associated with More Severe Disease? .............................................................. 172
Nauman Arif Jadoon, Zeeshan Butt, Ahmed Shahzad, Kamran Musthak
### 12. Liver Failure, Acute

<table>
<thead>
<tr>
<th>Paper Number</th>
<th>Title</th>
<th>Authors</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE-108</td>
<td>A Case of Hepatogastric Fistula as a Rare Complication of Pyogenic Liver Abscess</td>
<td>Suyyoung Lee, Chang Wook Kim, Hee Yeon Kim</td>
<td>172</td>
</tr>
<tr>
<td>PE-109</td>
<td>Investigation of Hepatocyte Induced by Direct Reprogramming as Novel Therapeutic Tool for Liver Regeneration and Cirrhosis</td>
<td>Su Hyun Park, Seo Yeon Hwang, So Hee Kang, Se Ra Yang, Seo Hyun Shin, Jongsiu Kim, Yong Han Paik</td>
<td>172</td>
</tr>
<tr>
<td>PE-110</td>
<td>Dynamic Risk Prediction of Hepatocellular Carcinoma Development Using Risk Prediction Models in Patients with Chronic Hepatitis B</td>
<td>Mi Young Jeon, Hye Won Lee, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Seung Up Kim</td>
<td>173</td>
</tr>
<tr>
<td>PE-111</td>
<td>MELD Score and Liver Stiffness Are Predictive for the Development of Acute Decompensation that Induce Acute-on Chronic Liver Failure</td>
<td>Yoo Li Lim, Moon Young Kim, Soon Koo Bak, Sang Ok Kwon</td>
<td>173</td>
</tr>
<tr>
<td>PE-112</td>
<td>Features of Care the Pregnant Woman after Liver Transplantation</td>
<td>Abdolat Snajdub, Daskal Marlen, Rymakhanov Myltykbay, Taganova Aliya, Kulmaganbetov Aidak, Sedakhmetov Achkmet, Daskaliev Zhaksylyk</td>
<td>174</td>
</tr>
<tr>
<td>PE-113</td>
<td>A Case of Acute Fatty Liver of Pregnancy Combined with Acute A Viral Hepatitis</td>
<td>Hyung Bin Yul, Tae Hye Lee, Suk Hyun Jang, Min J Park, Sun Hee Oh, Ki Hyun Rhyu, Hoon Sup Koo, Kyung Ho Song, Sun Moon Kim, Kyu Chun Huh, Young Woo Choi, Young Woo Kang</td>
<td>174</td>
</tr>
<tr>
<td>PE-114</td>
<td>A Case of HELLP Combined with AFLP</td>
<td>Suk Hyun Jang, Tae Hye Lee, Hyung Bin Yul, Min J Park, Sun Hee Oh, Ki Hyun Rhyu, Kyung Ho Song, Sun Moon Koo, Sun Moon Kim, Kyu Chun Huh, Young Woo Choi, Young Woo Kang</td>
<td>175</td>
</tr>
<tr>
<td>PE-115</td>
<td>Prevalence and Predictors of Thrombocytopenia in Advanced Liver Disease</td>
<td>Nauman Arif Jadoon, Zeeshan Butt, Saat U Khan, Kamran Mushtaq</td>
<td>175</td>
</tr>
</tbody>
</table>

### 13. Liver Transplantation

<table>
<thead>
<tr>
<th>Paper Number</th>
<th>Title</th>
<th>Authors</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE-116</td>
<td>Acute Graft versus Host Disease Following Deceased Donor Liver Transplantation: A Case Report</td>
<td>Jae do Yang, Hye Chul Yu</td>
<td>175</td>
</tr>
<tr>
<td>PE-117</td>
<td>Transplant Program Development in Kazakhstan: Experience of 6 Years</td>
<td>Melis Asykbayev, Gani Kutymuratov, Lyazzat Abdakhmanova, Yermakhan Assykhanyu, Alymkul Ashimkhana, Kakharman Yesemembetov, Saskarim Abdugaffarov</td>
<td>176</td>
</tr>
<tr>
<td>PE-118</td>
<td>Pediatric Liver Transplantation Experience in Kazakhstan</td>
<td>Gani Kutymuratov, Damir Zhelezhayev, Daulat Mustafinov, Alymkul Ashimkhana</td>
<td>176</td>
</tr>
<tr>
<td>PE-119</td>
<td>The First Successful Case of Living Donor Liver Transplantation in Jeju-do</td>
<td>Young-Kyu Kim, Kyu Hee Her, Byung-Chool Song</td>
<td>177</td>
</tr>
<tr>
<td>PE-120</td>
<td>Prognostic Value of Change in Muscle Area on Serial Preoperative Abdominal CT Studies in Liver Transplantation</td>
<td>Woo Kyoung Jeong, Jisun Lee, Young Kon Kim, Dongil Choi, Won Jae Lee</td>
<td>177</td>
</tr>
<tr>
<td>PE-121</td>
<td>De Novo Hepatitis B Virus Infection after Liver Transplantation in Hepatitis B Core-positive Recipients Using Hepatitis B Core-negativeRAFTs</td>
<td>Jon 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, Kyung-Suk Suh</td>
<td>177</td>
</tr>
<tr>
<td>PE-122</td>
<td>Splenic Artery Steal Syndrome after Orthotopic Liver Transplantation</td>
<td>Saktarim Abdugaffarov, Gani Kutymuratov, Tokan Sulhanliyev, Mukhanov Adbik, Zhekimbyayev Askan, Kakharman Yeemembetov, Yermakhan Assykhanyu, Alymkul Ashimkhana, Bashanlay Kaster, Melis Asykbayev</td>
<td>178</td>
</tr>
<tr>
<td>PE-123</td>
<td>LSRL</td>
<td>Hyeyoung Kim, Kwang-Woong Lee, Nam-joon Yi, Hae Won Lee, YoungRok Choi, Hyo-Sin Kim, Kyung Chul Yoon, Suk Kyun Hong, Rovgaliyev B, Kyung-Suk Suh</td>
<td>178</td>
</tr>
<tr>
<td>PE-124</td>
<td>Cost-effectiveness and Convenience of Myrept® 500 mg Tablet in Recipients after Liver Transplantation</td>
<td>Marco Sumo, Suk Kyun Hong, Kwang-Woong Lee, Suk-Won Suh, Nam-Joon Yi, Hyeyoung Kim, Jaehong Jeong, Kyungchul Yoon, Hye-Sin Kim, Kyung-Suk Suh</td>
<td>179</td>
</tr>
<tr>
<td>PE-125</td>
<td>Splenic Artery Embolization after Adult-to-adult Liver Transplantation</td>
<td>Rymakhanov M, Daskal A, Baygenzhina A, Daskaliev Zh</td>
<td>179</td>
</tr>
<tr>
<td>PE-126</td>
<td>Immunosuppression after Liver Transplantation</td>
<td>Kulmaganbetov A, Daskal M, Baygenzhina A, Daskaliev Zh</td>
<td>180</td>
</tr>
<tr>
<td>PE-127</td>
<td>Alterations of Hepatocellular Bile Salt Transporters and Effects of Immunosuppressants after Warm Ischemic Injury in Rats</td>
<td>Boldbaatar Mjasar, Hyeyoung Kim, Kwang-Woong Lee, Seung Cheol Oh, Guan Hong, Nam-Joon Yi, Hae Won Lee, YoungRok Choi, Suk-Won Suh, Jaehong Jeong, Suk Kyun Hong, Kyungchul Yoon, Hye-Sin Kim, Kyung-Suk Suh</td>
<td>180</td>
</tr>
<tr>
<td>PE-128</td>
<td>The Correlation between Pre-operative Volumetry and Real Graft Weight: Comparison of Two Volumetry Programs</td>
<td>Nadir Mussin, Kwang-Woong Lee, Hyeyoung Kim, Hyosin Kim, Nam-joon Yi, Kyung-Suk Suh, Soltangereev Eran</td>
<td>180</td>
</tr>
</tbody>
</table>
PE-149  Association of Serum Aminotransferases with High Density Lipoprotein Cholesterol (HDL-C) in Diabetic Patients  
Nirmal Prasad Bhatt, Nirajan Shrestha, Sudimma Dahal, Rojeet Shrestha  

16. NAFLD, Clinical  
PE-150  Association of Consumption Level of Simple Sugar and Aspartate and Alanine Aminotransferase: A Cross Sectional Observational Study  
Tae Yong Jung, Dae Won Jun, Joo Hyun Sohn, Jae Yoon Jeeong, Chang Hong Lee, Hye Jin Kang, Hye young Lee  
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  
Hyo Young Lee, Dae Won Jun, Hyunwoo Oh, Waqar Khalid Saeed, Jae Yoon Jeeong, Joo Hyun Sohn, Chang Hong Lee, Hyun Jung Kim, Hyeong Sik Ahn  
PE-152  Development of a Novel Simple Model for Predicting NASH in a Huge Biopsy-proven NAFLD Cohort  
Soo-Kyung Lim, Won Kim, Dong Hyeon Lee, Se Kyung Ju, Yong Jin Jung, Ji Won Kim, Byeong Giwan Kim, Kook Jae Lee  
PE-153  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  
Myeong Su Chu, Hyeon Jeong Yun, Myeong Jun Song, Seung Won Jung, Young Seok Kim, Si Hyun Bae, Jong Young Choi, Sang Wook Choi, Seung Kew Yoon  

17. Other Surgical Issues  
PE-154  Surgical Treatment of Liver Alveococcosis  
Dzhussubaliev Yerbol, Gani Kuyumzarov, Tokan Sulmanov, Mukazhanov Adibek, Zheksembayev Asan, Yermakhan Asykolayuly, Melis Asykolayuly, Shamenov Abylakhana  
PE-155  The Predicting Factors for Mortality after Hip Surgery in Cirrhotic Patients  
Sung Hee Yoon, Ji Won Park, Sung Eun Kim, Hyeong Su Kim, Myoung Kuk Jang, Dong Joa Kim, Sang Hoon Park, Myeong Seok Lee, Choong Kee Park  
PE-156  Results of Involving of “Roncoleukin” in Autologous Erythrocyte Shells in Patients with Surgical Sepsis (In Vitro Study)  
Erlan Sultangereev, Tagulov E.A., Aidzhan U.T., Mussin N.M.  
PE-157  Surgery for Metachronous Liver Metastases from Stomach Cancer  
Sung Hyun Kim, Dae Hoon Han, Gi Hong Choi, Jin-Sub Choi  
PE-158  Damage Control Measures in Major Liver Trauma  
Muhammad Zakria, Umar Aki  
PE-159  Laparoscopic Bile Duct Exploration with Glissonian Approach and Individual Dissection (Laparoscopic Glissonian Approach : Bile Duct Exploration Using Combination of Glissonian Approach and Individual Dissection)  
Sam-Youl Yoon, Myung-Jun Han, Jin-Suk Lee, Tae-Jin Song  
PE-160  Robotic ALPPS in a Patient with Cecal Cancer and Multiple Liver Metastasis (with Video)  
Jae Park, Gi Hong Choi, Jin Sub Choi  

18. Others  
PE-161  Estimation of Willingness to Pay for a Quality-adjusted Life Year on a Cure  
Hyn Jin Kyung Lee  
PE-162  The Degree of Liver Fibrosis Assessed Using Transient Elastography Independently Correlates with the Risk of Stroke: A Case-control Study  
Young Dae Kim, Dong Bum Song, Ji Hoe Heo, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoan Ahn, Ki Hang Hyeob Han, Ki Wang Joa Kim, Seung Up Kim  
PE-163  Association Liver Enzymes with Blood Pressure in Diabetic Patients  
Shrestha Royjet, Shrestha Nirajan, Bhatt Nirmal Prasad, Dahal Sudimma  
PE-164  Impact of Ledipasvir/Sofosbuvir on the Work Productivity of Chronic Hepatitis C Patients in Asia  
Young-Suk Lim, Henry Li Yuan Chien, Yock Young Dan, Mei Hsuan Lee, Eliza Kruger, Seng Tan, Zobbair M. Younossi  
PE-165  Pyloric Gland Adenoma of the Common Bile Duct: A Case Report and Review of Literature  
Gian Carlo Carpio, Guinevere T. Ang, Albert E. Israel  
PE-166  The Role of Endoscopic Ultrasound in a Tertiary Hospital: Past and Present  
Gian Carlo A. Carpio, Ramon E. Carpio, Frederick T. Dy  
PE-167  High Prevalence of Comorbidities and Contraindicated Medications in HCV Patients in Japan  
Hiroshi Yotsuyanagi, Eliza Kruger, Seng Tan
Contents

Ja Yoon Heo, Soo Young Park, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Won Young Tak, Young Oh Kweon, Kwang-Hyub Han, Seung Up Kim

PE-169  Validation of a Diagnostic Strategy of Combining Liver Stiffness Value by Transient Elastography and Enhanced Liver Fibrosis to Assess Fibrotic Burden in Patients with Chronic Hepatitis B ........................................................................................................... 199
Ja Yoon Heo, Beom Kyung Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, Kwang-Hyub Han, Seung Up Kim

PE-170  Body Mass Index as a Predictor of Severity of Fibrosis from a Tertiary Liver Center in the Philippines .......................................................... 199
Angelo Lozada, Catherine Teh

PE-171  Recurrence Patterns of Curative Resected Ampulla of Vater Cancer: Significance of Lymph Node Dissection around Superior Mesentery Artery 200
Hongbeom Kim, Jae Ri Kim, Wooil Kwon, Jin-Young Jang, Sun-Whe Kim

Basic Science Workshop 1  Intra and Extracellular Vesicle: Cell to Cell Cross Talk in the Liver

Exosome .................................................................................................................................................. 203
Yong Song Gho

Exosome and Liver Disease ...................................................................................................................... 204
Yong-Han Paik

Role of Autophagy in Liver Injury .......................................................................................................... 205
Wen-Xing Ding

Basic Science Workshop 2  Intra and Extracellular Vesicle: Cell to Cell Cross Talk in the Liver

Autophagy in Chronic Viral Hepatitis .................................................................................................. 209
Seong-Jun Kim

Regulation of Inflammasome Signaling and Its Potential Link to Metabolic Disorders ................... 210
Je-Wook Yu

Inflammasome in Liver Disease .......................................................................................................... 211
Jong Eun Yeon

Clinical Science Methodology Workshop 1  Real World Experience from Expert

MELD: From an Idea to a Practice ....................................................................................................... 217
W. Ray Kim

RCT: From an Idea into a Practice ...................................................................................................... 218
Young-Suk Lim

Cohort Study: From an Idea into a Practice .......................................................................................... 219
Jeong Won Jang

Clinical Science Methodology Workshop 2  Real World Experience from Expert

From an Idea into a New Device: MR Elastography ........................................................................ 223
Kengo Yoshimitsu

From an Idea into a New Drug: Oltipraz ............................................................................................ 224
Yoon Jun Kim

How to Prove Cost-effectiveness in My Research ............................................................................. 225
Jeonghoon Ahn

Symposium 1  Hepatitis C Virus

Appropriate Application of Direct Acting Antivirals ..................................................................... 229
Mark Sulkowski

Current Strategy for Chronic Hepatitis C Treatment in Korea ......................................................... 231
Sook-Hyang Jeong
Towards IFN-free Treatment: DCV+ASV for Genotype 1 - Sang Hoon Ahn 233
Management of Direct Antiviral Agent Failures - Maria Buti 237

**Special Lecture 1.**

Acute Kidney Injury in Cirrhosis - Florence Wong 245

**Clinical Hepatology Update**

Clinical Hepatology Update: Changes of DDLT Waiting Priority in Korea - Myoung Soo Kim 251
Diagnosis of Sub-centimeter Sized Hepatocellular Carcinoma - Young Kon Kim 252
Nonalcoholic Steatohepatitis: Diagnosis and Treatment Update - Dae Won Jun 256
Hepatitis C Virus: One Pill Is Enough for All Genotype - Ki Tae Yoon 263
Hepatitis B Virus: Changing Antiviral Treatment Strategies: Low Viral Load in Liver Cirrhosis with Hepatitis B Virus - Dong Hyun Sinn 267

**Special Interest Group Symposium 1** Nonalcoholic Fatty Liver Disease (NAFLD): Non-obese NAFLD Patients

Difference between Western and Eastern NAFLD Patients - Eiji Miyoshi 271
Clinical Differences between Obese and Non-obese NAFLD Patients - Sang Hoon Park 272
Genetic Aspects of Non-obese NAFLD Patients - Luca Valenti 275
Therapeutic Approach in Non-obese NAFLD Patients - Jin-Woo Lee 276
Hepatic Lipid and Glucose Metabolism in NAFLD - Douglas G. Marlek 277

**KLTS Symposium 1** How to Minimize Living Donor’s Damage and Maximize Living Donor’s Safety?

Intra-operative Management for Donor Safety during Laparoscopic Donor Hepatectomy - Choon Hyuck David Kwon 281
Early Experience of Robotic Donor Hepatectomy: Learn from Pioneer - Gi Hong Choi 283
Post-donated Complications after Donor Hepatectomy: Achilles Heel of Donor Surgeon - Young Seok Han 284
Fate of Live Donor after Liver Donation: Physician’s View - Dong Hyun Sinn 285

**KLTS Symposium 2** How Far Extended Criteria for Advanced Hepatocellular Carcinoma in Liver Transplantation?

Is Zero Recurrence Possible?: Predictor of Recurrence after Liver Transplantation for Hepatocellular Carcinoma - Hae Won Lee 289
Acceptable Guidelines of Liver Transplantation for Advanced Hepatocellular Carcinoma - Chong Woo Chu 291
## Contents

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Transplantation for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis</td>
<td>292</td>
</tr>
<tr>
<td>Jong Man Kim</td>
<td></td>
</tr>
<tr>
<td>Adjuvant Therapy for Prevention of Recurrence of Hepatocellular Carcinoma after Liver Transplantation</td>
<td>293</td>
</tr>
<tr>
<td>Jae Min Chun</td>
<td></td>
</tr>
<tr>
<td>Multi- and Inter-disciplinary Approach for Recurrent Hepatocellular Carcinoma</td>
<td>294</td>
</tr>
<tr>
<td>Dong Jin Joo</td>
<td></td>
</tr>
<tr>
<td><strong>KASL-KLCA Joint Symposium</strong> Cure of Hepatitis B Virus and Hepatocellular Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Carcinoma: Immune Check Point Blockade</td>
<td>297</td>
</tr>
<tr>
<td>Andrew X. Zhu</td>
<td></td>
</tr>
<tr>
<td>Immune Engineering toward a Cure of Hepatitis B Virus</td>
<td>298</td>
</tr>
<tr>
<td>Su-Hyung Park</td>
<td></td>
</tr>
<tr>
<td>New Therapeutic Perspectives for Hepatitis B Virus Cure</td>
<td>299</td>
</tr>
<tr>
<td>Jia-Horng Kao</td>
<td></td>
</tr>
<tr>
<td>Predictive Molecular Pathology in Hepatocellular Carcinoma: In the Era of Targeted Therapy</td>
<td>300</td>
</tr>
<tr>
<td>Jo-Seog Lee</td>
<td></td>
</tr>
<tr>
<td><strong>Multidisciplinary Approach to Patients with Transarterial Chemoembolization Failure</strong></td>
<td></td>
</tr>
<tr>
<td>Transarterial Chemoembolization Refractoriness / Failure</td>
<td>303</td>
</tr>
<tr>
<td>Joong-Won Park</td>
<td></td>
</tr>
<tr>
<td>Rescue Therapies for Transarterial Chemoembolization Failure and Clinical Outcomes</td>
<td>304</td>
</tr>
<tr>
<td>Josep M. Llovet</td>
<td></td>
</tr>
<tr>
<td>Radiation Therapy as a Potential Modality for Patients with Transcatether Arterial Chemoembolization Failure</td>
<td>305</td>
</tr>
<tr>
<td>Mi-Sook Kim</td>
<td></td>
</tr>
<tr>
<td><strong>KLCA-KHBPS Joint Symposium</strong> Optimal Management of Recurrent Hepatocellular Carcinoma after Resection</td>
<td></td>
</tr>
<tr>
<td>Follow-up Protocol after Resection: Risk-based or Unified</td>
<td>309</td>
</tr>
<tr>
<td>Shin Hwang</td>
<td></td>
</tr>
<tr>
<td>Locoregional Therapy for Recurrent Hepatocellular Carcinoma after Resection</td>
<td>310</td>
</tr>
<tr>
<td>Ji Hoon Kim</td>
<td></td>
</tr>
<tr>
<td>Re-resection: Indication and Limitation</td>
<td>315</td>
</tr>
<tr>
<td>Kyung Sik Kim</td>
<td></td>
</tr>
<tr>
<td>Salvage Liver Transplantation: Role and Limitation, Optimal Patient Selection</td>
<td>318</td>
</tr>
<tr>
<td>Choon Hyuck David Kwon</td>
<td></td>
</tr>
<tr>
<td>Rebuttal with Case Discussion</td>
<td>320</td>
</tr>
<tr>
<td>Jeong Heo</td>
<td></td>
</tr>
<tr>
<td><strong>Korea Central Cancer Registry</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular Carcinoma Random Sample Analysis Report</td>
<td>323</td>
</tr>
<tr>
<td>Young-Suk Lim</td>
<td></td>
</tr>
<tr>
<td><strong>Emerging Therapies for Hepatocellular Carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td>Searching for Biomarker-driven Therapy for Hepatocellular Carcinoma</td>
<td>327</td>
</tr>
<tr>
<td>Si Hyun Bae, Jung-Hee Kwon, Jin Young Park</td>
<td></td>
</tr>
<tr>
<td>Molecular Targeted Therapy for Hepatocellular Carcinoma: Learning from Genome-matched Trials in Other Solid Cancers</td>
<td>328</td>
</tr>
<tr>
<td>Jee Hyun Lee</td>
<td></td>
</tr>
<tr>
<td>Advances in Percutaneous Ablation Therapies for Hepatocellular Carcinoma</td>
<td>329</td>
</tr>
<tr>
<td>Won Young Tak</td>
<td></td>
</tr>
</tbody>
</table>

www.theliverweek.org xxxvii
**KLTS Coordinator Session**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative Evaluation of Living Donor Candidate for Liver Transplantation</td>
<td>Sanghee Song, Ok Kyung Kim, Myung Eun Lee, Jin Yong Choi, Hyeyoung Kim, Sung-Woo Ahn, Hyo-Sin Kim, Kyung Chul Yoon, Suk Kyun Hong, Nam-Joon Yi, Kwang-Woong Lee, Kyung-Suk Suh</td>
</tr>
<tr>
<td>Education and Counselling for Living Donor for Liver Transplantation</td>
<td>Sunyoung Son</td>
</tr>
<tr>
<td>Preparation for Emergency Liver Transplantation</td>
<td>Ji Yeon Park</td>
</tr>
<tr>
<td>Immuno Suppression after Liver Transplantation</td>
<td>Jeong Hee Kang</td>
</tr>
</tbody>
</table>

**Symposium 2  Pros and Cons of LC-Controversial Issues**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonelective Beta Blocker: Hemodynamic Effects vs. Non-hemodynamic Effects</td>
<td>Moon Young Kim</td>
</tr>
<tr>
<td>Scoring Systems for Alcoholic Hepatitis</td>
<td>Patrick S. Kamath</td>
</tr>
<tr>
<td>Anticoagulation: Do or Avoid?</td>
<td>Erica Villa</td>
</tr>
<tr>
<td>Albumin: New Roles beyond Volume Expander</td>
<td>Samuel S. Lee</td>
</tr>
</tbody>
</table>

**Special Lecture 2**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C Virus: Next Generation of DAAs</td>
<td>Mark Sulkowski</td>
</tr>
</tbody>
</table>

**Special Interest Group Symposium 2  Cirrhosis with Portal Hypertension: Liver-Heart-Kidney Axis, from Portal Hypertension to Hyperdynamic Circulatory Syndrome**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Diagnosis of Acute Kidney Injury in Cirrhosis: The Reasonable Cut-off Serum Creatinine Value</td>
<td>Florence Wong</td>
</tr>
<tr>
<td>The Current Management of Acute Kidney Injury in Cirrhosis</td>
<td>Seong Won Jeong</td>
</tr>
<tr>
<td>Role of Heart in Refractory Ascites, Acute Kidney Injury and Hepatorenal Syndrome</td>
<td>Samuel S. Lee</td>
</tr>
<tr>
<td>The Liver in Cardiac Disease</td>
<td>Patrick S. Kamath</td>
</tr>
</tbody>
</table>

**KHPBS-KLTS Joint Symposium  How Can We Overcome Complicated Portal Vein?**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication or Contraindication of Liver Transplantation in Patient with Portal Vein Thrombosis</td>
<td>Nam-Joon Yi</td>
</tr>
<tr>
<td>Anatomical Reconstruction</td>
<td>Gyu-Seong Choi</td>
</tr>
<tr>
<td>How to Overcome Complicated Portal Vein Thrombosis? Extra-anatomic Bypass</td>
<td>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</td>
</tr>
<tr>
<td>Intervention for Complicated Portal Vein</td>
<td>Gi-Young Ko</td>
</tr>
</tbody>
</table>
## Contents

**KHBPS-JSHBPS Joint Symposium 1  Evidence Based Management for Hepatocellular Carcinoma**

- Primary Liver Cancer Registry in Japan: How Has It Been Evolving? .................................................. 371
  Norihiro Kokudo
- Random Sampling of Korea Central Cancer Registry for Hepatocellular Carcinoma .......................... 372
  Young-Suk Lim
- What and How to Build Up Solid Evidences for Surgical Treatment of Hepatocellular Carcinoma .......... 373
  Choon Hyuck David Kwon

**KHBPS-JSHBPS Joint Symposium 2  Incorporating Recent Technologies in Liver Surgery**

- Laparoscopic and Robotic Liver Resection Using Advanced 3D Liver Simulation Software .................. 377
  Atsushi Sugio, Yutaro Kato, Yoshinari Tanahashi, Tadashi Kagawa, Masayuki Kojima, Sanae Nakajima, Syo-ichiro Tsuji, Ichiro Uyama
- Laparoscopic Liver Resection Using 3D Camera System ........................................................................ 378
  Kyung-Suk Suh
- Application of Indocyanine Green Fluorescence Imaging in Liver Resection ...................................... 379
  Norihiro Kokudo, Yoshikuni Kawaguchi
- Liver Resection Using Robotic System .................................................................................................. 380
  Gi Hong Choi

**Symposium 3  Nonalcoholic Fatty Liver Disease (NAFLD)**

- Lipid Droplet as a Potential Target for Nonalcoholic Fatty Liver Disease ........................................... 383
  Douglas G. Mashek
- Noninvasive Diagnostic Method of Nonalcoholic Steatohepatitis ......................................................... 384
  Eiji Miyoshi
- Hepatocellular Carcinoma Development in Nonalcoholic Fatty Liver Disease .................................. 385
  Luca Valenti
- Molecular Targets for Nonalcoholic Steatohepatitis Therapeutics ....................................................... 386
  Yong Kyun Cho
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.)
Virus-induced IFN-α4 Potently Blocks IFN-α Signaling by ISG15-USP18 in HCV Infection: Implication for Increased IFN Responsiveness after DAA Treatment

Pil Soo Sung1,3, Seon-Hui Hong1, Su-Hyung Park2, Eui-Cheol Shin1

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Aims: IFN-α4 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-α4 protein due to a premature stop codon, is associated with a favorable treatment response while the IFNL4-DG genotype coding for functional IFN-α4 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 investigated the biological effects of IFN-α4 and its responsiveness after DAA therapy. Furthermore, we studied the effects of DAA treatment on the induction of IFN-α4 and IFN responsiveness.

Methods: Primary human hepatocytes (PHHs) were infected with JFH1 HCVcc at high titer. Hepatoma cells were transfected with IFNL4-expressing plasmid various experiments were performed to identify the biological effects of IFN-α4.

Results: JFH1 HCVcc infection induced IFN-α4 gene expression in PHHs. After IFNL4 gene transfection in hepatoma cells, IFN-α4 protein was scarcely detected in culture supernatant as previously reported. However, IFN-α4 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 responsiveness was confirmed by transfection of siRNAs for ISG15 and/or USP18. This potent activity of IFN-α4 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-α5 including IFN-α4 and restored the IFN responsiveness.

Conclusions: The current data demonstrate that virus-induced IFN-α4 potently induces ISG15/USP18-mediated IFN-α unresponsiveness. Our data clearly demonstrate that HCV-infected hepatocytes restore IFN responsiveness after DAA therapy.

Keywords: IFN-α4, Hepatitis C virus, USP18, DAA

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


1School of Medicine, Johns Hopkins University, Baltimore, MD, USA. 2The Chinese University of Hong Kong, Hong Kong. 3Toronto Western Hospital Liver Centre, Toronto, Ontario, Canada. 4Institute of Liver Studies, Kings College Hospital, London, UK. 5Hospital Henri Mondor, Université Paris-Est, Créteil, France. 6Beaujon Hospital, University Paris Diderot, INSERM UMR 1149, Paris, France. 7Ruane Medical and Liver Health Institute, Los Angeles, California, USA. 8Ludwig-Maximilians-Universität, Munich, Germany. 9Université d’Auvergne, Clermont Ferrand, France. 10Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy. 11University of Hong Kong, Hong Kong. 12Santa Maria Ammanniata Hospital, Firenze, Italy. 13CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. 14University of British Columbia, Vancouver, British Columbia. 15University of Alberta, Edmonton, Alberta, Canada. 16Southern California Permanente Medical Group, Los Angeles, Los Angeles, CA, USA. 17Gedars-Sinai Medical Center, Los Angeles, CA, USA. 18Gilad Sciences, Inc. Foster City, CA, USA. 19Mount Sinai Beth Israel Medical Center, NY, USA. 20Johann Wolfgang Goethe University Medical Center, Frankfurt, Germany

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/RBV treatment due to adverse-events.

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

---

**PS 1-3**

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

Sandzhak Abdullaliev14, T.M. Welzel2, J. Petersen2, K. Herzer2, P. Ferenci4,
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Peck-Radosavljevic13, Y. Zhao14, M.J. Jimenez-Exposito14, S. Zeuzem1

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3Universitätsklinikum Essen (AöR), Essen, Germany; 4Medizinische
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6Medizinische Hochschule Hannover, Hannover, Germany; 7Center for
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9Universitätsklinikum Bonn, Bonn, Germany; 10Karinum Krankenhaus,
Stockholm, Sweden; 11Academic Medical Center, University of
Amsterdam, Amsterdam, Netherlands, 12Universitätsklinikum Würzburg,
Würzburg, Germany; 13Klinikum Klangenfurt, Klangenfurt, Austria; 14Bristol-Myers
Squibb, Princeton, NJ

**Aims:** The all-oral, pan-genotypic combination of daclatasvir+sofosbu-
vir+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 physi-
cian’s choice. The primary efficacy outcome was SVR12.

**Results:** Efficacy data were available for 436485 patients enrolled.
Most patients were HCV treatment experienced (70%) with median
HCV RNA 5.5 log10 IU/mL. 388 (80%) patients had confirmed cir-
rhosis (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 without/with ribavirin and comparable across
HCV GT, presence of cirrhosis, liver transplant status, HIV coinfection,
and other baseline characteristics. There were 28 deaths over treat-
ment or follow-up (none considered treatment-related), 91 experi-
enced serious adverse events (11 considered treatment-related), and
38 discontinued treatment or died due to adverse events (10 treat-
ment-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.

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**PS 1-4**

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

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**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 biochemical 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 0.659 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-F4) 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

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**PS 1-5**

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

**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 examined 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

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**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

**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 HBsAg-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 HBsAg-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-
Recent Advances 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, Chung Hyun Kim, Hyo-Sin Kim, Hyeyoung Kim, Youngrok Choi, Kwang-Woong Lee, Sung Ho Choi, Tae Ho Hong, Young Kyoung You, Dong Goo Kim

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
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.
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.)
PS 2-1

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

Young-Suk Lim1, Si-Hyun Bae2, Sang Hoon Ahn3, Hyung Joon Kim3, Won Young Tak4, Kwan Sik Lee5, Maria Buti6, Edward Gane7, Wai Kay Seto8, Henry LY Chan10, Wan-Long Chuang11, Tatjana Stepanova12, Aric-Josun Hui13, Rajiv Mehta14, Harry Janssen15, 16, SK Acharya17, John F Flaherty18, Benedetta Massetto19, Andrea Catcath20, Phillip Dinh21, G Mani Subramanian22, John G McHutchison23, Calvin Pan24, Maurizia Brunetto20, Namiki Izumi21, Patrick Marcellin22

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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

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Table. Efficacy and Safety at Week 48

<table>
<thead>
<tr>
<th>n/N (%)</th>
<th>TAF (N=285)</th>
<th>TDF (N=140)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;29 IU/mL</td>
<td>268/285 (94)</td>
<td>130/140 (92.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>ALT normalization (centrallaboratory)</td>
<td>196/236 (83.1)</td>
<td>91/121 (75.2)</td>
<td>0.076</td>
</tr>
<tr>
<td>ALT normalization (AASLD criteria)</td>
<td>137/276 (49.6)</td>
<td>44/138 (31.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip BMD, mean (SD) % change (g/cm²)</td>
<td>-0.29 (2.14)</td>
<td>-2.16 (2.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spine BMD, mean (SD) % change (g/cm²)</td>
<td>-0.88 (2.86)</td>
<td>-2.51 (3.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sCr, mean (SD) change (mg/dL)</td>
<td>0.01 (0.09)</td>
<td>0.02 (0.10)</td>
<td>0.32</td>
</tr>
<tr>
<td>Proteinuria (dipstick)</td>
<td>54/282 (19.2)</td>
<td>26/140 (18.5)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Efficacy results are missing = failure; 1ULN43U/mL, 2ULN34U/mL, 3ULN19U/mL, 4ULN19U/mL; 5sCr is serum creatinine; 6eGFRCG=CLCr(Cockcroft-Gaultmethod)

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PS 2-2

Entecavir versus Lamivudine for Prevention of Liver-related Events in Patients with HBV-related 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, adeovir 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%), varical 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

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**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 filtration 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. S1Cr-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 <38.5cm^2/m^2 for women and <52.4cm^2/m^2 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±0.9 mg/dl, and the mean eGFR was 81.8±25.8 ml/min by MDRD and 87.3±29.9 ml/min by cystatin C. The mean mGFR was 76.0±26.6 ml/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

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**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
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 differed significantly from that of cirrhosis group (1.00 ± 1.68 vs -1.27 ± 3.17, p=0.001) and 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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1Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 2Department of Biomedical sciences and Nuclear Medicine, Cancer Research Institute, Seoul National University College of Medicine, 3Department of Gastroenterology and Hepatology, Soonchunhyang University Bucheon Hospital

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

Jun Ho Lee1, Neung Hwa Park2, Hyun Je Kang1, Jae Hee Suh2, Chang Jae Kim1, Hwan Hee Lee1, Soo Youn Choi1, Whaseon Lee-Kwon1, and Hyug Moo Kwon1

1School of Life Sciences, Ulsan National Institute of Science and Technology, Ulsan, Republic of Korea, 2Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea

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 (C57BL/6 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 +/- or...
Specimens were archived before sorafenib treatment and a candidate database. It was tested with in vitro shRNA experiments for its effect on mRNA expression analysis between sorafenib-sensitive and resistant (HCC) are still not available, despite the modest benefit of sorafenib.

**Aims:**

- g14/g145/g148/g135/g131/g3
- June 16-18, 2016
- Jae-Kyung Won1, 2, 3, §, Su Jong Yu4, §, Chae Young Hwang1, Joong-Won nib Responsiveness in Patients with Hepatocellular Carcinoma
- EDN1 Expression as a Novel Biomarker for Predicting Sorafenib Responsiveness

**Results:**

- 14
- 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

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**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

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**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) selecting 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](image-url)
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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 6.2X10^6 IU/mL.

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

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 reimbursement 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 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 - 005

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

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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 (251/1,143 patients, 1.9% at 5-years, $P<0.001$). The AUROC for the HCC development at 3/5 years was 0.780.73, 0.790.78, and 0.790.76 for cirrhosis, APRI and FIB-4, among overall cohort, respectively, and was 0.730.83 and 0.830.89 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
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/ADV combination therapy in patients with LAM-resistant chronic hepatitis B infection.

Methods: One hundred ninety-seven patients received LAM plus ADV, and 28 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 patients with baseline HBV DNA level > 10^4 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 < 10^4 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 < 10^4 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

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 covertly 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...
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

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

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*Corresponding author

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
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:** Administering 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

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**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

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**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/FH1 HCV plasmid with or without luciferase gene. After In
Asian Patients with Genotype 1 HCV Achieve 99% SVR with 12 Weeks of Ledipasvir/Sofosbuvir: Integrated Analysis of Phase 3 Studies

Young-Suk Lim, Sang Hoon Ahn, Kwan Sik Lee, Seung Woon Paik, Yoon-Jae Lee, Soo-Hyang Jeong, Ju-Hyun Kim, Seung Kew Yoon, Hyung Joon Yim, Won Young Tak, Sang-Young Han, Jenny C. Yang, Shampa De-Oertel, Hongmei Mo, Bing Gao, Yoon Jun Kim, Kwan-SoO Byun, Young Seok Kim, Jeong Heo, Jia-Horng Kao, Wan-Long Chuang, Masashi Mизолами, Masao Omata, Kwang-Hyub Han

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

Sang Hoon Ahn, Young-Suk Lim, Kwan Sik Lee, Seung Woon Paik, Yoon-Jae Lee, Soo-Hyang Jeong, Ju-Hyun Kim, Seung Kew Yoon, Hyung Joon Yim, Won Young Tak, Sang-Young Han, Jenny C. Yang, Shampa De-Oertel, Hongmei Mo, Bing Gao, Yoon Jun Kim, Kwan-SoO Byun, Young Seok Kim, Jeong Heo, Jia-Horng Kao, Wan-Long Chuang, Masashi Mизолами, Masao Omata, Kwang-Hyub Han

Keywords: Ledipasvir, Sofosbuvir, Asian, Genotype 1
Integrated Safety and Tolerability of Daclatasvir plus Asunaprevir in Patients with Chronic HCV Genotype 1b Infection

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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 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
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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 an independent risk factor for HCC development (adjusted hazard ratio [HR] = 2.55) and overall mortality (adjusted HR = 3.69) on multivariate analysis. 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, Hepatocellular carcinoma, Mortality

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**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 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 35,597 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%, 76.9%, 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
Resistance-associated variants

Keywords: tasvir and asunaprevir for genotype 1b chronic hepatitis C.

monitor the baseline variants before the combination therapy of daclatasvir and asunaprevir for genotype 1b chronic hepatitis C and investigate clinical features. So it would be important to recognize drug-resistant variants before treatment is not well known yet in the Koran population.

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.

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

<table>
<thead>
<tr>
<th>HCV RAV</th>
<th>L31</th>
<th>Y93</th>
<th>HCV RAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (%)</td>
<td>13 (2.9)</td>
<td>39 (8.7)</td>
<td>51 (11.4)</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>427 (92.4)</td>
<td>388 (86.6)</td>
<td>376 (83.9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>HCV RAV</th>
<th>Positive (%)</th>
<th>Negative (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>male</td>
<td>28 (12.9)</td>
<td>189 (87.1)</td>
</tr>
<tr>
<td>female</td>
<td>23 (11.0)</td>
<td>187 (89.0)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>61 ± 10</td>
<td>61 ± 10</td>
<td>0.535</td>
</tr>
<tr>
<td>Age group</td>
<td>-39</td>
<td>1 (20.0)</td>
<td>4 (80.0)</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>3 (5.5)</td>
<td>52 (94.5)</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>18 (13.3)</td>
<td>117 (86.7)</td>
</tr>
<tr>
<td></td>
<td>60-69</td>
<td>17 (13.6)</td>
<td>108 (86.4)</td>
</tr>
<tr>
<td></td>
<td>70-79</td>
<td>12 (11.2)</td>
<td>95 (88.8)</td>
</tr>
<tr>
<td>Examination date</td>
<td>2015/09/01~</td>
<td>2015/08/31</td>
<td></td>
</tr>
<tr>
<td>Laboratory data (mean ± SD)</td>
<td>65.9 ± 43.2</td>
<td>64.8 ± 42.6</td>
<td>0.855</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>51.8 ± 45.7</td>
<td>47.0 ± 45.8</td>
<td>0.485</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>0.9 ± 0.4</td>
<td>0.9 ± 0.6</td>
<td>0.617</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>145.4 ± 66.0</td>
<td>151.7 ± 64.4</td>
<td>0.522</td>
</tr>
<tr>
<td>Platelet (×10^3/mm^3/μL)</td>
<td>2.3 ± 3.7</td>
<td>2.2 ± 2.4</td>
<td>0.763</td>
</tr>
<tr>
<td>Liver disease</td>
<td>chronic hepatitis</td>
<td>23 (13.3)</td>
<td>181 (88.7)</td>
</tr>
<tr>
<td></td>
<td>compensated LC</td>
<td>26 (12.5)</td>
<td>182 (87.5)</td>
</tr>
<tr>
<td></td>
<td>decompensated LC</td>
<td>2 (13.3)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>HCC</td>
<td>no</td>
<td>39 (11.0)</td>
<td>316 (89.0)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>12 (16.7)</td>
<td>60 (83.3)</td>
</tr>
<tr>
<td>Past treatment</td>
<td>naive</td>
<td>32 (12.0)</td>
<td>235 (88.0)</td>
</tr>
<tr>
<td></td>
<td>experience</td>
<td>19 (11.9)</td>
<td>141 (88.1)</td>
</tr>
<tr>
<td>Past treatment response</td>
<td>intolerance</td>
<td>3 (12.5)</td>
<td>21 (87.5)</td>
</tr>
<tr>
<td></td>
<td>null response</td>
<td>2 (5.1)</td>
<td>37 (94.9)</td>
</tr>
<tr>
<td></td>
<td>partial response</td>
<td>2 (15.4)</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td></td>
<td>relapse</td>
<td>12 (14.3)</td>
<td>72 (85.7)</td>
</tr>
</tbody>
</table>

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

T. Garimella, T. Eley, M. Bifano, Y. Gandhi, F. LaCreta, R. Bertz, M. AbuTarif

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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.

Conclusion: 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.

Keywords: DAA, HCV, Renal impairment

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. NSSA-Y93H and NSSA-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-naive and -experienced patients from mainland China, Korea, and Taiwan. Similar Japanese data (4 studies; n=445) were pooled for comparison. SVR12 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 NSSA sequences were available for 282 patients (126 mainland Chinese [45%], 80 Koreans [28%], 76 Taiwanese [27%]). NSSA-Y93H and/or L31 RAPs were observed pre-treatment 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 similar with 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 NSSA-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, NSSA polymorphisms, Daclatasvir, Asunaprevir, Chinese, Koreans, Taiwanese

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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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6Auckland Clinical Studies Ltd, Auckland, New Zealand

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 HB 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 HBcAb negative at screening 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 HB DNA and retested for HBsAg if HB 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 HB 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

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3. NAFLD, Clinical

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

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

O - 021
Hye Won Lee, Beom Kyung Kim, Seung Up Kim, Do Young Kim, Non-invasive Markers for Assessing Fibrosis in Korean The Accuracy of Transient Elastography and Comparison of

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, ARFI, 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, 0.8-0.962). 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 - 023

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

Sang Bong Ahn, Dae Won Jun, Jae Yoon Jeong, Joo Hyun Sohn, and Chang Hong Lee

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 characteristic (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
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

Sae Kyung Joo, Koo Bo Kyung, and Won Kim

Department of Internal Medicine, Seoul National University College of Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center

**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 ASM (P<0.001) compare to without advanced fibrosis. Meanwhile, there were no significant differences in BMI, total body fat mass, TAT amount, and ASM 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-MIS) 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
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 underROC 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 CAP (adjusted E). However, specificity (for ≥F3, 52.94%; for F4, 84.66% in TE) was markedly improved after adjustment for CAP without diminishing 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.
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, is 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 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 (≥100 mg/dL), and estimated glomerular filtration rate (GFR) (all P < 0.05), and seemed to be associated with hypertension and body mass index (≥25 kg/m²) (all P < 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 P < 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). AUROC 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
Efficacy and Safety at Week 48

<table>
<thead>
<tr>
<th></th>
<th>TAF (N=581)</th>
<th>TDF (N=292)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt;2 IU/mL</td>
<td>371/581 (63.9)</td>
<td>195/292 (66.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>ALT normalization (centrallaboratory)</td>
<td>384/537 (71.5)</td>
<td>179/268 (68.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>ALT normalization (AASLD criteria)</td>
<td>257/572 (44.9)</td>
<td>105/290 (36.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>3/576 (0.5)</td>
<td>0</td>
<td>0.22</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
<td>58/565 (10)</td>
<td>23/285 (8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hip BMD, mean (SD) % change (g/cm²)</td>
<td>-0.10 (2.29)</td>
<td>-1.72 (2.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spine BMD, mean (SD) % change (g/cm²)</td>
<td>-0.42 (2.93)</td>
<td>-2.29 (3.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sCr, mean (SD) change (mg/dL)</td>
<td>0.01 (0.12)</td>
<td>0.03 (0.10)</td>
<td>0.020</td>
</tr>
<tr>
<td>Proteinuria (dipstick) %</td>
<td>158/577 (27.4)</td>
<td>65/286 (22.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>eGFRcr, mean (SD) change (mL/min)</td>
<td>-0.3 (14.5)</td>
<td>-4.7 (13.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Efficacy results are missing = failure

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 <2 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; eGFRcrG, 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
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Aims: Tenofivir (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 HBeAg 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/ADV 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

Switching Tenofivir 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 tenofivir 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 with 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/M/A (n=73), rtS202G (n=64), rtM204V/L (n=17), rtA181V/T (n=97), rtN236T (n=39), rtL180M (n=157), and rtM250L/V (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 (1.8±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: Tenofivir, Combination therapy, Hepatitis B virus, Resistance
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 positive. 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 over 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 1.25% were observed.

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

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. Proporation 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 >24 kPa 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
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, multidadrug-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 naive 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

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

Young-Suk Lim, Henry Lai Yuen Chan, Yock Young Duan, Mei Hsuan Lee, Ming-Lung Yu, Marta Silva, Jorge Felix, Zohair M. Younossi

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, CHC-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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of new cases in a n=10,000 cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCC</td>
</tr>
<tr>
<td>Taiwan</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF 12 wks</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>1,702</td>
</tr>
<tr>
<td>No treatment</td>
<td>2,697</td>
</tr>
<tr>
<td>Korea</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF 12 wks</td>
<td>72</td>
</tr>
<tr>
<td>PR</td>
<td>2,014</td>
</tr>
<tr>
<td>No treatment</td>
<td>3,404</td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF 12 wks</td>
<td>69</td>
</tr>
<tr>
<td>PR</td>
<td>2,168</td>
</tr>
<tr>
<td>No treatment</td>
<td>3,681</td>
</tr>
<tr>
<td>Hong Kong</td>
<td></td>
</tr>
<tr>
<td>LDV/SOF 12 wks</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>2,228</td>
</tr>
<tr>
<td>No treatment</td>
<td>3,794</td>
</tr>
</tbody>
</table>

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-naive 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 reduced by 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 naive, firstly diagnosed CHC were enrolled from 7 tertiary hospitals in Korea from Jan 2008 to Dec 2011. Among them, 473 (38.8%) 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 IU/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?

Kwang Il Seo, Byung Chul Yun*, Byung Hoon Han, Sang Uk Lee and Eun Taek Park

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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 non-treatment of chronic hepatitis C.

Results: 1277 patients were checked Anti-HCV or HCV RNA. 108 patients did not check 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 efficiency/safety of daclatasvir (pan-genotypic NSSA 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 NSSA 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 NSSA 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 89% 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

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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

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

Ju Hyun Lee, Junhyeon Cho, Sanghyuk Im, Beom Hee Kim, Chung Seop Lee, Jung Wha Chung, Yung Jung Kim1, Eun Sun Jang, Jin-Wook Kim, Hong Bin Kim, Soo-Hyang Jeong
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**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

Hye Won Oh1,2, Ra Ri Cha1, Sang Soo Lee1,2, Chang Min Lee1, Wan Soo Kim1,2, Hyun Chin Cho1, Jin Joo Kim3, Jae Min Lee1,2, Hong Jun Kim1,2, Chang Yoon Ha1, Hyun Jin Kim1,2, Tae Hyo Kim1,2, Woon Tae Jung1,2, Ok Jae Lee1,2

National University, Seongnam, Republic of Korea

**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 employee)-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

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**O - 048**

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

Yang Jae Yoo, Ji Hoon Kim1, Young-Sun Lee, Jihye Je, Sang Jun Suh, Young Kuk Jung, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun

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

**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 eighty 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, dadatasir plus asunaprevir showed comparable efficacy and safety with previous clinical studies. More data in large population are needed including SVR results.

**Keywords:** Dadatasir, Asunaprevir, HCV

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**The Liver Week 2016**

**6. Liver Cirrhosis, Clinical**

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

**O - 049**

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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1 Internal Medicine, Korea University College of Medicine, Ansan, 2 Internal Medicine, Korea University College of Medicine, Seoul, 3 Internal Medicine, Kyungpook National University School of Medicine, Daegu, 4 Internal Medicine, Soonchunhyang University College of Medicine, Seoul, 5 Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, 6 Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, 7 Internal Medicine, Sungkyunkwan University College of Medicine, 8 Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, South

**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.

**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

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**O - 050**

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

Yoo Li Lim1, Ki Tae Suk2, Jung-Hwan Yoon3, Moon Young Kim1, Chang Wook Kim4, Ja Kyung Kim5, Hana Park6, Seong Gyu Hwang7, Byung Seok Lee8, Sae Hwan Lee9, Hong Soo Kim8, Jae Young Jang9, Chang Hyeong Lee10, Byung SeokKim10, Yoon Ok Jang1, Mee Yong Cho11, Eun Sun Jung12, Yong Man Kim13, Si Hyun Bae14, Soon Koo Baik15

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

Chien-Chang Liao, Ta-Liang Chen
Department of Anesthesiology, School of Medicine, Taipei Medical University

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 5×10^7 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 Picrosinus-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

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

<table>
<thead>
<tr>
<th></th>
<th>n Person-years</th>
<th>Events</th>
<th>Incidence*</th>
<th>HR  (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>15764</td>
<td>95430</td>
<td>1641</td>
<td>17.2</td>
</tr>
<tr>
<td>LC</td>
<td>3941</td>
<td>23221</td>
<td>675</td>
<td>29.1</td>
</tr>
<tr>
<td>Female</td>
<td>No LC</td>
<td>4980</td>
<td>29405</td>
<td>718</td>
</tr>
<tr>
<td>Male</td>
<td>No LC</td>
<td>1245</td>
<td>7352</td>
<td>249</td>
</tr>
<tr>
<td>Age, 20-39</td>
<td>No LC</td>
<td>10784</td>
<td>66025</td>
<td>923</td>
</tr>
<tr>
<td>Age, 40-49</td>
<td>No LC</td>
<td>2696</td>
<td>15869</td>
<td>426</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>LC</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day in-hospital mortality</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Septicemia</td>
<td>2.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Medical expenditure, USD</td>
<td>2247±2651</td>
<td>2479±2775</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>8.7±4.5</td>
<td>9.6±6.5</td>
</tr>
</tbody>
</table>

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. Follow-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 60082 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

<table>
<thead>
<tr>
<th>n</th>
<th>30-day in-hospital adverse events*</th>
<th>Incidence, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female†</td>
<td>No LC</td>
<td>285435</td>
<td>10039</td>
</tr>
<tr>
<td>Male†</td>
<td>No LC</td>
<td>308592</td>
<td>14657</td>
</tr>
<tr>
<td>20-29 years‡</td>
<td>No LC</td>
<td>68067</td>
<td>1751</td>
</tr>
<tr>
<td>30-39 years‡</td>
<td>No LC</td>
<td>61255</td>
<td>1556</td>
</tr>
<tr>
<td>40-49 years‡</td>
<td>No LC</td>
<td>73366</td>
<td>2038</td>
</tr>
<tr>
<td>50-59 years‡</td>
<td>No LC</td>
<td>94790</td>
<td>2758</td>
</tr>
<tr>
<td>60-69 years‡</td>
<td>No LC</td>
<td>82847</td>
<td>3046</td>
</tr>
<tr>
<td>≥70 years‡</td>
<td>No LC</td>
<td>213702</td>
<td>13547</td>
</tr>
<tr>
<td>Fracture with surgery</td>
<td>No LC</td>
<td>400566</td>
<td>3334</td>
</tr>
<tr>
<td>TBI</td>
<td>No LC</td>
<td>109696</td>
<td>8157</td>
</tr>
<tr>
<td>Neck and trunk fracture</td>
<td>No LC</td>
<td>88832</td>
<td>4553</td>
</tr>
<tr>
<td>Upper limb fracture</td>
<td>No LC</td>
<td>218907</td>
<td>4219</td>
</tr>
<tr>
<td>Lower limb fracture</td>
<td>No LC</td>
<td>279792</td>
<td>13075</td>
</tr>
</tbody>
</table>

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, sepsis, 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

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

Young Youn Cho, Jeong-Hoon Lee*, Young Chang, Joon Yeul Nam, Hyeky Cho, Seong Hee Kang, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon

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

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 varical 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.

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 recurrent 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

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

Soung Won Jeong1, Tae Yeob Kim2, Eileen L. Yoon3, Do Seon Song4, Hee Yeon Kim5, Chang Wook Kim6, Young Kul Jung7, Dong Hyun Sinn8, Sang Gyune Kim9, Jae Young Jang10, Won Kim11, Hwi Young Kim12, Moon Young Kim13, Eunhee Choi14, Dong Joon Kim15

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

O - 052

O - 053
Cystatin C Is Better than Creatinine for Predicting Prognosis in Cirrhotic Patients with Sarcopenia

Han Ah Lee, Seung Woon Park, Sang Jung Park, Tae Hyung Kim, Sang Jun Suh, Young Kal Jung, Ji Hoon Kim, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um, Yeon Seok Seo
Department of Internal Medicine, Korus University College of Medicine, Seoul, Korea

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 TMPT/height <16.8 mm/m.

Results: A total of 245 patients were enrolled. Age was 55.0±10.2 years and 159 years (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/mL, P=0.970). During 23±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

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

Meegun Hong1, Ki Tae Suk1, Yunhee Yeong Lee1, Chulho Kim2, Hui Chul Choi2, Chang Seok Bang1, Jai Hoon Yoon1, Gwang Ho Balik2, Dong Joon Kim1, Min Uk Jang2, Jong Hee Sohn2

1Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, South Korea, 2Department of Neurology, Hallym University College of Medicine, Chuncheon, South Korea

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

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**O - 056**

Rifaximin Prolongs Overall Survival in Cirrhotic Patients Experiencing Hepatic Encephalopathy

Seong Hee Kang1, Jeong-Ju Yoo2, Jeong-Hoon Lee3, Yun Bin Lee4, Young Youn Cho1, Hyelsi Cho1, Eun Ju Cho1, Su Jong Yu1, Yoon Jun Kim1, Jung-Hwan Yoon1

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Department of Gastroenterology and Hepatology, Soonchunhyang University Hospital Bucheon, Department of Gastroenterology and Hepatology, Bundang Cha Hospital

**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% C.Ia=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=0.267, 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.difficle-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

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**O - 057**

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

Galam Leem1, Jun Yong Park1,2, Beom Kyung Kim1,2, Seung Up Kim1,2, Do Young Kim1,2, Sang Hoong Ahn1,2, Kwang-Hyub Han1,2

1Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, 2Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea, 3Yonsei Liver Center, Yonsei University Health System, Seoul, Korea

**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-existing treatment response criteria 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, RB-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-existing 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 predict poor prognosis of patients accurately. This would provide us useful long-term prognostic information and make individualized management possible.

**Keywords:** Treatment response, Rotterdam criterion, PBC, Prognosis prediction

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**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**

Sang Gyune Kim1, Jeong-Ju Yoo1, Young Seok Kim1, Bora Lee2, Soung Ligation and Non-selective Beta-blockers

**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). 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 was 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

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**7. Liver Transplantation**

**O - 059**

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

Nam-Joon Yi3, Sanghee Song1, Ok-Kyoung Kim1, Hyeyeong Kim2, Suk Ryun Hong1, Kyung Chul Youn4, Hye-Sin Kim1, Youngrok Choi2, Hae Won Lee2, Kwang-Woon Lee5, Kyung-Suk Suh2

1Organ Transplantation Center, Seoul National University Hospital; 2Department of Surgery, Seoul National University College of Medicine, Korea

**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 weight ratio (DRWR) was 1.12 (0.56–1.95); the DRWR>10.0 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 pro-thrombin 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.
Renal Function Difference between Anti-hepatitis B Immunoglobulin (HBIG) Monotherapy and HBIG Combined with Entecavir

Jae Geun Lee1,2, Juhan Lee1,2, Jung Jun Lee3, Seung Hwan Song3, Jee Youn Lee1, Su-kyung Kwon1, Myoung Soo Kim1,2, Man Ji Ju1,2, Gi Hong Choi1,2, Jin Sub Choi1,2, and Soon Il Kim1,2

1Department of Surgery, and 2The Research Institute for Transplantation, Yonsei University College of Medicine, Seoul, Korea. 3Department of Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea

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 38.9±56.8 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

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

Soo In Seo, Kwang-Woong Lee1, Seung Cheol Oh, Min Young Park, Sohee Kim, Nam-Joon Yi, Kyung-Suk Suh

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

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 intravenous 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 autophagosome.

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 autophagosome in the cytoplasm.

Re-endothelialization of Decellularized Porcine Liver Prevent Thrombosis

Jong Man Kim, Jisoo Lee, Kyung-Sik Kim, Nuri Lee, Chan-Woo Cho, Gyu-Seong Choi, Choon Hyuck David Kwon, Jae-Won Joh
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)carbodiimide 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

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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 incompatible (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 ABOc and ABOi LT.

Results: Clinical characteristics 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).

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

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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 selection criterion for LT to predict long-term outcome 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 patients who 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, >3 cm 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:** Hepatocellular carcinoma, Liver transplantation, Recurrence, TACE

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**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.

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**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 (ATG) 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

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**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.
Characterization of Cholangiocarcinoma-like Hepatocellular Carcinoma Using Gene Expression Pattern Analysis
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Aims: Hepatocellular 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

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 endocannabinoids, endocannabinoid-degrading enzymes and endocannabinoid receptors, was determined in healthy liver and tumors. Diethylamino-methylindole-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

Keywords:
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

EK11 (Epha2 Kinase Inhibitor 1) Suppresses Tumor Growth in Hepatocellular Carcinoma and Cholangiocarcinoma by Inducing Autophagy 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 seborrheic 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 autophagy 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 EKI1 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 autophagy 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% O2, 5% CO2, 94% N2. 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-acetyllysotine 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
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 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

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

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**Table. Diagnostic performance for distinguishing fibrosis stage IV**

<table>
<thead>
<tr>
<th>Variable</th>
<th>F4 vs. Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPV</td>
<td>0.905</td>
</tr>
<tr>
<td>ACC</td>
<td>0.891</td>
</tr>
<tr>
<td>PPV</td>
<td>0.851</td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>0.851</td>
</tr>
</tbody>
</table>

Abbreviation: THR, threshold; SEN, sensitivity; SPE, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

1 Threshold was computed by Youden's index. Sensitivity, specificity, accuracy, PPV and NPV were calculated from the threshold and the 95% CI of AUC by using Delong's method. All other p-values were compared using the McNemar test and all other p-values were corrected by Bonferroni's method.

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**O - 078**

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

Min Yeong Kim, Joo Hyun Sohn, Tae Yeob Kim

**Methods:** Total 431 patients whose SV was measured by ultrasonography (length x height x width x 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, 339/7.8%/75/17.4%/17/3.9%), fibrosis stage (F0/F1/F2/F3/F4, 358/1.1%/404/3.0%/66/16.0%/56/12.9%/23/53.6%). 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±219), F3 (236±79), F4 (457±283). AUROCs of SV and SV/BSA 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/BSA for the diagnosis of cirrhosis were 268ml, 161ml respectively.

**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
Aims: 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, and FIB-4 score were statistically significant to predict, and with estimating the area under the receiver operating characteristic curve (AUC) 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 count, LSM, 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 M2BP level significantly correlated with ELF score (rs = 0.1764, P < 0.0001) and FibroScan measurements (rs = 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

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**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 analyzes 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

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 alpha-fetoprotein (AFP), and 75 mAU/mL for des-γ-carboxy prothrombin (DCP); there was no correlation among these three factors (r=0.237, p=0.000). The 1-, 2-, 3-, and 5-year rates were 22.4%, 34.4%, 47.1%, 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, MM, 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.

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 (CR: 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 recurrence 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

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

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 <100,000, 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**

**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 Gq-coupled receptors such as angiotensin II and endothelin-1 receptors. Gq-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 stellate cell
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 hepatitis 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 CXCL3 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 receptor (RLR) signaling, interferon regulatory factor 3, in HAV-infected cells. Moreover, these chemokines were significantly increased in the sera of acute hepatitis A patients. The production of IFN-α was reduced by silencing the expression of RIG-I-like receptor (RLR) signaling molecules, such as mitochondrial antiviral signaling protein and interferon regulatory factor 3, in HAV-infected cells.

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-α was also robustly induced by HAV infection, and the blocking of secreted IFN-α partially abrogated the production of CCL4 and CCL5 in HAV-infected cells. However, CXCL10 production was not decreased by the blocking of IFN-α. 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 T cell-associated chemokines, particularly CXCL10 via RLR signaling, even without secreted IFNs.

Keywords: Hepatitis A virus, CXCL10, IRF3, IFN-α.
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 immunosorbent 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.

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
Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon*, Young-Sun Lee, Eunjung Ko, Yang Jae Yoo, Jihye Je, Sang Jun Suh, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon*, and Kwan Soo Byun

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-CSF 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), metionine 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~12th 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-CSF was injected once a month. 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-CSF expression increased significantly in HF (14.7 times), alcoholic hepatitis (7.1 times), chronic thiocitoacetamide (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, HMGC-CoA reductase) and inflammatory markers (MCP-1 TNF-a). G-CSF treatment increased cell proliferation markers (p-R3 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 in G-CSF group but decreased in G-CSF+PA group. 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

The Liver Week 2016

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Methods: direct effect of G-CSF on hepatocytes in NAFLD. G-CSF expression was suggested via marrow stem cell mobilization. We investigated the direct effect of G-CSF on hepatocytes in NAFLD. 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.
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, a-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 NAFLD from simple steatosis.

**Keywords:** Exosome, NASH, NAFLD

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**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

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**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 as DMSO. The third group was administered with MCD diet +0.7% DMSO. Lorcaserin (10 mg/kg) was given daily by oral gavage for 6 weeks. 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 mice. MCD diet +lorcaserin-treated mice compared with MCD diet +DMSO-treated controls. 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-alcoholic 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 palmitic 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, palmitic 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, HNF4α, 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 GMA-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 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+GMA-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

O - 096

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

June 18, 2016 | 16:30-17:40
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Purpose: Laparoscopic anatomical liver resection still present s major technical difficulties, such as pedicle control. The extrahepatic glissonian 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 glissonian 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. 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 perioperatively 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°C) 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 each 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°C), 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 recurrences.

Figure 1. Intraoperative view of transduodenal surgical ampullectomy.
the detailed indication of TSA for adenocarcinoma of AoV is needed. Not always correct in detecting adenocarcinoma. More study to define be a good substitute for PD even though preoperative biopsy was not always correct in detecting adenocarcinoma. Study more to define the detailed indication of TSA for adenocarcinoma of AoV is needed.

**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.

O - 101

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 pancreatectoduodenectomy (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

O - 102

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

O - 103

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 eradication 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 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

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**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 factors 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). Aspartate 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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**O - 105**

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-
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 ± 1.01, 5.03 ± 0.89, and 4.44 ± 0.83, respectively. Diastolic blood viscosities (DBV) were 16.65 ± 3.78, 15.98 ± 3.23, and 13.81 ± 3.30, respectively. These results indicate 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 results 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

### Table 1. Comparison of WBV by liver parenchymal status

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Fatty liver (n=46)</th>
<th>Chronic hepatitis (n=70)</th>
<th>Liver cirrhosis (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBV (cP)</td>
<td></td>
<td>5.25 ± 1.01</td>
<td>5.03 ± 0.89</td>
<td>4.44 ± 0.83</td>
</tr>
<tr>
<td>DBV (cP)</td>
<td></td>
<td>16.65 ± 3.78</td>
<td>15.98 ± 3.23</td>
<td>13.81 ± 3.30</td>
</tr>
</tbody>
</table>

* WBV: whole blood viscosity

Methods: To generate iHeps, mouse embryonic fibroblasts (5x10^4 cells) were transduced with pMX retroviruses expressing individual hepatic transcription factors, Hnf4α 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 dominantly 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 storage 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.

### O - 107

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

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Objective: It is well known that the degrees of liver fibrosis, portal hypertension, residual liver volume are crucial factors for post-hepatectomy 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/Bwt) 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...

www.theliverweek.org 69
counts was lower (121.0 vs. 168.5 \times 10^9/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 \leq 138 \times 10^9/L (Exp(b)=14.812, 95% CI: 2.771-79.181, p=0.002) and RLV/TFLV \leq 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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**O - 108**

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

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

Wang Yong Choi, Woo Jin Chang, Byoung Kuk Jang, Jae Seok Hwang, Sang Jin Kim, Heon Ju Lee, Moon Joo Hwang, Young Oh Kweon, Won Young Tak, Soo Young Park, Su Hyun Lee, Chang Hyeong Lee, Byung Seok Kim, Si Hye Kim, Jeong Ill Suh, Jun Gi Park and Daegu-Gyeongbuk Liver Study Group (DGLSG)

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 diagnosis 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 diagnosis as cirrhosis. Mean time to diagnose HCC were 4.98±3.29, 4.37±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 diagnosis 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

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 available 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 were significantly lower 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
O - 111
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 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 1.161, 95% CI 1.79-6.38).

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

O - 112
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

O - 113
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. 3.8%, p<0.001).

Keywords: Hepatitis B virus, Entecavir, Tenofovir, Maintained virological response, Virological failure, Virological response, Cohort, Retrospective, Liver cirrhosis, Liver cancer, Survival
Table 1. Scoring system for the prediction of sorafenib response and overall survival.

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

### 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).
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 miRNA (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, Sorafenib, Response, Prediction, Prognostic marker, Disease free survival, LT-free survival, MicroRNA-21, MicroRNA-26a, MicroRNA-29a, Prognostic marker, Disease free survival.
**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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**O - 117**

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

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**O - 118**

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

HyukSoo Eun, Gee Young Yun, Byung Seok Lee, Jae Kyu Sung, Eaun Seok Lee, Hee Seok Moon, Sun Hyung Kang, Jong Seok Joo, Hae Jin Shin, Seok Hyun Kim

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

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2Department of Biomedical Engineering, Yonsei-Dong, Seoul 110-799 Korea; 3Interdisciplinary Program in Bioinformatics and 4Department of Statistics, Seoul National University, Daehak-dong, Seoul 151-742 Korea

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

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-, and 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<0.001). Univariate analysis identified tumor size and Child-Turcotte-Pugh (CTP) score as significant predictive factors for 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, patients with intermediate or advanced stage HCC were bridged to curative resection. 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

PO-001 ~ PO-006  Cell Biology and Basic
PO-007 ~ PO-012  HCV, Clinical
PO-013 ~ PO-018  Liver Cirrhosis
PO-019 ~ PO-023  NAFLD
PO-024 ~ PO-028  Liver Cirrhosis and Others
PO-029 ~ PO-034  HBV, Clinical
PO-035 ~ PO-039  HBV, Clinical
PO-040 ~ PO-044  HBV, Clinical
PO-045 ~ PO-049  Alcoholic Liver Disease and Others
PO-050 ~ PO-055  HCC, Basic
PO-056 ~ PO-061  HCC, Clinical
PO-062 ~ PO-067  HCC, Clinical
PO-068 ~ PO-073  HCC, Clinical
PO-074 ~ PO-078  HCC, Clinical
PO-079 ~ PO-084  HCC, Clinical
PO-085 ~ PO-089  Surgery
PO-090 ~ PO-093  Surgery
Establishment of Hepatoma Treatment Model Using Hepatoma Cell Spheroids

Han Seul Park1, Jae Young Jang1*, Seoung Won Jeong1, Sae Hwan Lee2, Hepatoma Cell Spheroids

Aims: Three dimensional (3D) spheroid cells are more closely mimic natural tissues and organs than cells grown in 2D. ‘Biocompatible spherical 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, 200μM) and Rg5 (10, 50, 100μM) 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 spheroids 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

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

Soo Jin Kim1, Kyu Hee Hwang1, Ji Hee Kim1, Moon Young Kim2, Soon Koo Baik2, Seung Ray Cha1, Ranjan Das3, Kyu Sang Park3

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

Regulation of Tumor Angiogenesis and Endothelial Mesenchymal Transition by Dickkopf-1

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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
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 VM-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 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 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-dioxygenase (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

Keywords: Hepatic stellate cells, IFN-gamma, 1-Methyl tryptophan

Image: Diagram showing the interaction of IFN-gamma with HSCs and its effects on cell cycle arrest and anti-fibrosis.
MicroRNA-99a Attenuates HCV Replication through the Downregulation of Subtilisin Kinase Isozyme-1 (SKI-1)/Site-1 Protease (S1P)

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Aims: MicroRNAs modulate various biological processes through dys-regulation 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 kinase isozyme-1/site-1 protease (SK1/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. SK1/S1P expression was significantly suppressed by treatment with miR-99a-5p mimics in HCV replicating cells. Regarding the role of SK1/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.

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Keywords: HCV, MicroRNA, MiR-99a, Lipid metabolism, Subtilisin kinase isozyme-1 (SKI-1)/ site-1 protease (S1P)
24 weeks. The primary endpoint was end of treatment response (ETR). Safety evaluations included adverse events.

**Results:** The incidence of NSSA 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 in 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 NSSA RAVs in Korea. Treatment was generally well-tolerated regardless of cirrhosis status.

**Keywords:** Daclatasvir, Asunaprevir, Real-life experience, Chronic hepatitis C, Genotype 1b

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**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. On-treatment virologic response showed undetectable RNA levels (less than 25 IU/mL) within 4 weeks 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
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. 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, NS5A inhibitor. We investigated the real-life prevalence of RAV against NS5A 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 NS5A 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
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 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 10^9/L), all other parameters were within the normal ranges (WBC - 7.89 x 10^9/L, Hb - 149 g/L, HCT - 41.9%, RBC - 4.63 x 10^12/L, PLT - 113 x 10^9/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 mmol/L, Total protein - 73.8 g/L, Albumin 43.4 g/L, Glucose - 5.37, Creatinine - 51 mmol/L, Ferritin - 179.7 ng/ml, Serum Fe - 19.34, APP - 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 3.4x10^6/mL, genotype - 1. GI endoscopy revealed esophageal varices stage 0-1, reflux esophagitis. Elastometry showed advanced fibrosis F4 by METAVIR, ECG showed no bradicardia, no arrhythmia in the past and current times. She was confirmed with a diagnosis of Chronic HCV induced Liver Cirrhosis, Child A-S. 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
Conclusions: subsequently developed AKI.

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 plasma 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 and urinary FABP might be useful biomarkers for early detection of AKI in cirrhosis.

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 - 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.
**PO - 016**

**Increased Risk of Bacterial Infection in Cirrhotic Patients with Acute Variceal Bleeding Who Were Treated with Prophylactic Rifaximin**

Wook Hyun Yeo, Eileen L. Yoon, Hyung Gi Bae, Yu Ri Hwang, Seong Eun Park, Jong Ho Lee, Ji Young Park, Jung Min Choi, Tae Joo Jeon, Won Chang Shin, Won-Choong Choi

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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. Methods: We reviewed 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. 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 1 month (p<0.001)/3 months (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

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**PO - 017**

**Cyanoacrylate Injection versus Band Ligation for the Treatment of Bleeding from Cardiac Varices on Lesser Curvature Side of the Stomach**

Sang Jung Park, Yeon Seok Seo, Seung Woon Park, Han Ah Lee, Tae Hyung Kim, Sang Jun Suh, Young Kul Jung, Ji Hoong Kim, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun, Soon Ho Um

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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. 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

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**PO - 018**

**Efficacy and Safety of Endoscopic Variceal Obliteration (EVO) vs. Balloon-occluded Retrograde Transvenous Obliteration (BRTO) as Prophylactic Treatment for Gastric Varices**

Jung Wan Choe1, Hyung Joon Yim1, Seung Hwa Lee2, Hwan Hoon Chung2, Sang Joon Suh1, Seung Young Kim1, Jong Jin Hyun1, Sung Woo Jung2, Young Kul Jung1, Ja Seol Koo1, Ji Hoong Kim1, Yeon Seok Seo1, Jong Eun Yeon1, Sang Woo Lee1, Kwan Soo Byun1, Soon Ho Um1

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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 point, 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

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**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

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**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 liver 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 were performed. LOXL2 levels were associated with initial fibrosis stages, and would predict fibrosis progression as assessed by ARFI.

**Results:** The AUROCs for predicting advanced fibrosis (F3) was 0.631 (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, OBGME
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±SD, 31.25±20.06 IU/L vs. 22.55±14.48 IU/L, P<0.001). The number of eligible patients 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.

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. 1H-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; 0.0.1.0, 1.0) 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); 1H MR spectroscopy (1H MRS); hepatic metabolites.

Keywords: Non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), 1H MR spectroscopy (1H 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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The Liver Week 2016
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

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 immunoblotting 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-labeling 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

Risk and Outcome of Stroke in Patients with Liver Cirrhosis: Two Nationwide Studies

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Keywords: Hepatic steatosis, Appendicular skeletal muscle mass, Sarcopenia, Insulin resistance

www.theliverweek.org 91
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. Using the Taiwan National Health Insurance Research Database, we identified 6944 adults aged 50-79 years who underwent colonoscopic polypectomy and were stratified by sex and age. We then compared patients with and without LC who underwent polypectomy at a single center between January 2006 and December 2015.

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 × 10^3/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 ooze and were controlled by hemostatic procedures using endoscopic hemoclips.

Keywords: Bleeding, Polypectomy, Liver Cirrhosis, Colonic polyp

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 per 1000 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

### Table 2. Incidence and adjusted hazard ratios of stroke in association with previous Liver Cirrhosis exacerbations by sex and age

<table>
<thead>
<tr>
<th>N</th>
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<th>PY</th>
<th>Incidence</th>
<th>HR (95% CI)</th>
</tr>
</thead>
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<td>No Liver Cirrhosis</td>
<td>27776</td>
<td>939</td>
<td>193140</td>
<td>4.9</td>
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<td>9100</td>
<td>0.3</td>
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<td>4</td>
<td>2190</td>
<td>1.8</td>
</tr>
<tr>
<td>30-39 years†</td>
<td>3716</td>
<td>20</td>
<td>28209</td>
<td>0.7</td>
</tr>
<tr>
<td>Liver Cirrhosis</td>
<td>929</td>
<td>23</td>
<td>5961</td>
<td>3.9</td>
</tr>
<tr>
<td>40-49 years†</td>
<td>6364</td>
<td>118</td>
<td>47211</td>
<td>2.5</td>
</tr>
<tr>
<td>Liver Cirrhosis</td>
<td>1591</td>
<td>72</td>
<td>9098</td>
<td>7.9</td>
</tr>
<tr>
<td>50-59 years†</td>
<td>6424</td>
<td>214</td>
<td>47001</td>
<td>4.6</td>
</tr>
<tr>
<td>Liver Cirrhosis</td>
<td>1606</td>
<td>63</td>
<td>8486</td>
<td>7.4</td>
</tr>
<tr>
<td>60-69 years†</td>
<td>5048</td>
<td>298</td>
<td>34977</td>
<td>8.5</td>
</tr>
<tr>
<td>Liver Cirrhosis</td>
<td>1262</td>
<td>55</td>
<td>5490</td>
<td>10.0</td>
</tr>
<tr>
<td>≥70 years†</td>
<td>5012</td>
<td>286</td>
<td>24251</td>
<td>10.7</td>
</tr>
</tbody>
</table>

PT, 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

<table>
<thead>
<tr>
<th></th>
<th>No liver cirrhosis</th>
<th>Liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>14174</td>
<td>7089</td>
</tr>
<tr>
<td>Mortality</td>
<td>751 (5.3)</td>
<td>629 (8.9)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>330 (2.3)</td>
<td>213 (3.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1286 (9.1)</td>
<td>665 (9.4)</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>5460 (38.5)</td>
<td>2932 (41.4)</td>
</tr>
<tr>
<td>Prolonged length of stay</td>
<td>13.58±21.08</td>
<td>12.61±15.52</td>
</tr>
<tr>
<td>Increased medical expenditure</td>
<td>3188±5624</td>
<td>3231±5254</td>
</tr>
</tbody>
</table>

*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 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-perf2a, 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

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**PO - 028**

Prevalence of Vitamin D Deficiency in Chronic Liver Disease at the Outpatient Clinics of the University of the Philippines-Philippine General Hospital

Aubrey Q. Taguba1, Mariel Dianne S. Velasco2, Mara Teresa T. Panlilio1, Maria Joanne M. Rubio1, Margaret Elaine J. Villamayor1, Janus P. Ong1, Ma. Lourdes O. Daez2

1Section of Gastroenterology, Department of Medicine, UP-Philippine General Hospital, 2Department of Medicine, UP-Philippine General Hospital

**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. STAFA SE version 12 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

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**PO - 029**

Treatment Outcomes of Long-term Tenofovir based Antiviral Therapy for Patients with Chronic Hepatitis B: A Single Center, Retrospective Cohort Study

In Suk Min, Ik Sang Shin, In Hee Kim, Chang Hun Lee, Seung Young Seo, Seong Hun Kim, Sang Wook Kim, Seung Ok Lee, Soo Teik Lee, Dae Ghon Kim

Department of Internal Medicine, Research Institute of Clinical Medicine, and Chonbuk National University Medical School and Hospital, Jeonju, Jeonbuk, South Korea

**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 (<20 IU/mL) 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 ≥ 4log10IU/mL (HR 0.22, 95% CI 0.10–0.46, P < 0.001), HBsAg-positive (HR 0.20, 95% CI 0.06–0.57, P = 0.008) 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 sign-
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 response, Treatment

PO - 030
Comparison of Long-term Efficacy of Tenofovir Monotherapy between Nucleos(t)ide-naive and Nucleos(t)ide-resistant Chronic Hepatitis B Patients

Young Min Shin, Kyung Hye Park, Seok Won Jung, Neung Hwa Park, Bo Ryung Park, Chang Jae Kim, Byung Uk Lee, Jae Ho Park, Byung Gyu Kim, In Du Jeong, Sung-Jo Bang, Jung Woo Shin

Aims: Tenofovir (TDF) is a nucleoside 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)-naive and NA-resistant chronic hepatitis B (CHB) patients.

Methods: Of the 540 eligible patients, 452 were NA-naive 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).

Conclusions: TDF was effective and safe for patients regardless of whether they were NA-naive or resistant. Especially, the lower HBV DNA levels at baseline, HBeAg-negative, and NA-naive patients were significantly associated with VR.

Keywords: Tenofovir, Nucleos(t)ide analog-naive, Nucleos(t)ide-resistance, Chronic hepatitis B

PO - 031
Obesity and Hepatocellular Carcinoma in Patients Receiving Entecavir for Chronic Hepatitis B

Jaemin Lee, Sun Hong Yoo, Sang Jong Park, Young Min Park, Won Sohn
Department of Internal Medicine, and Liver Center, Bundang Jeaeng Hospital

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 Jeaeng 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/mm3 (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/m2 (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 cm2 (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

Woo Jin Jung, Jae Young Jang, Soung Won Jeong, Sae Hwan Lee, Sang Gyune Kim, Sang-Woo Cha, Young Seok Kim, Young Deok Cho, Hong Soo Kim, Boo Sung Kim, Suyeon Park

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 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

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**PO - 033**

Clinical Course of Partial Virologic Responders under Prolonged Tenofovir Therapy in Nuclos(t)ides-naïve Patients with Chronic Hepatitis B

Young Min Shin, Kyung Hye Park, Seok Won Jung, Neung Hwa Park, Young Min Shin

Department of Internal Medicine, Korea University College of Medicine

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
Impact of Antiviral Therapy with Tenofovir or Entecavir on Renal Function in Patients with Hepatitis B Virus-related Cirrhosis

Jihye Park1,3, Kyu Sik Jung1,3, Beom Kyung Kim1,2,3, Seung Up Kim1,2,3, Do Young Kim1,2,3, Sang Hoon Ahn1,2,3, Kwang-Hyub Han1,2,3 and Jun Yong Park1,2,3

Department of Internal Medicine1, Institute of Gastroenterology2, Yonsei University College of Medicine, Seoul, Korea, Yonsei Liver Center, Severance Hospital3

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 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 monotherapy (n=22), TDF/LAM (n=49), or TDF/ETV combination therapy (n=62) for more than 6 months. Viral 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

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

Baek Gyu Jun1,‡, Hyuk Jin Moon*, Sae Hwan Lee†, Hong Soo Kim§, Sang Gyune Kim‡, Young Seok Kim‡, Boo Sung Kim‡, Soung Won Jeong‡, Jae Young Jung‡, Young Don Kim§, Gab Jin Cheon§

1Department of Internal Medicine, Soonchunhyang University College of Medicine Cheonan Hospital, Cheonan, South Korea, 2Department of
Internal Medicine, Soochunhyang University College of Medicine Bucheon Hospital, Bucheon, South Korea, 2Department of Internal Medicine, Soochunhyang University College of Medicine Seoul Hospital, Seoul, South Korea, 3Department of Internal Medicine, University of Ulsan College of Medicine, Gangneung Asan Hospital, Gangneung, South Korea

**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 2 (3.5%) in Group B (p=0.01). 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 ± 0.21 mg/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 ± 0.16 mg/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

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**Table 1. Patient Baseline Characteristics**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>ADF</th>
<th>ADF with LMV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>41</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>49.9±9.5</td>
<td>48.3±10.0</td>
<td>0.436</td>
</tr>
<tr>
<td>Male sex</td>
<td>29/12</td>
<td>39/18</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.1±18</td>
<td>73.6±15.7</td>
<td>0.068</td>
</tr>
<tr>
<td>HBeAg-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline serum creatinine (mg/dL)</td>
<td>0.79±0.16</td>
<td>0.75±0.15</td>
<td>0.245</td>
</tr>
<tr>
<td>Baseline eGFR (mL/minute)</td>
<td>102±17</td>
<td>108±16</td>
<td>0.083</td>
</tr>
<tr>
<td>Baseline phosphate</td>
<td>3.24±0.71</td>
<td>3.27±0.64</td>
<td>0.798</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>172.2±38.0</td>
<td>123.0±162.5</td>
<td>0.520</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1.03±0.49</td>
<td>1.11±0.69</td>
<td>0.576</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.52±0.427</td>
<td>4.53±0.422</td>
<td>0.919</td>
</tr>
<tr>
<td>HBV DNA, log10 IU/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis(%)</td>
<td>7(17.1)</td>
<td>10(17.5)</td>
<td>0.952</td>
</tr>
<tr>
<td>HTN</td>
<td>3(7.3)</td>
<td>7(12.3)</td>
<td>0.514</td>
</tr>
<tr>
<td>DM</td>
<td>0(0)</td>
<td>1(1.8%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>ADF</th>
<th>ADF with LMV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increase by &gt;0.3</td>
<td>1(2.4%)</td>
<td>7(12.3%)</td>
<td>0.134</td>
</tr>
<tr>
<td>Creatinine increase by &gt;0.5</td>
<td>0(0)</td>
<td>2(3.5%)</td>
<td>0.508</td>
</tr>
<tr>
<td>Creatinine increase by &gt;0.3-0.5</td>
<td>1(2.4%)</td>
<td>5(8.8%)</td>
<td>0.396</td>
</tr>
<tr>
<td>eGFR decrease by &gt;30%</td>
<td>1(5.9%)</td>
<td>6(10.5%)</td>
<td>0.566</td>
</tr>
<tr>
<td>eGFR decrease by 30-50%</td>
<td>1(2.4%)</td>
<td>3(5.3%)</td>
<td>0.638</td>
</tr>
<tr>
<td>eGFR decrease by &gt;50%</td>
<td>0(0%)</td>
<td>3(5.3%)</td>
<td>0.262</td>
</tr>
<tr>
<td>Total hypophosphatemia</td>
<td>11(26.8%)</td>
<td>14(24.6%)</td>
<td>0.799</td>
</tr>
<tr>
<td>Transient hypophosphatemia</td>
<td>8(19.5%)</td>
<td>9(15.8%)</td>
<td>0.631</td>
</tr>
<tr>
<td>Persistent hypophosphatemia</td>
<td>3(7.3%)</td>
<td>5(8.8%)</td>
<td>0.795</td>
</tr>
</tbody>
</table>

**Keywords:** Lamivudine, Adefovir dipivoxil, Renal function, 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. NBR was achieved 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 (range from 22 to 99 months). In univariate Cox regression analysis, platelet count (<150 x 10³/mm³; HR 4.71; 95% CI 1.70-15.92; 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

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 (<40 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. Virolological 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
with ETV plus TDF combination therapy. Resistance types before combination treatment were LMV only resistance, ETV resistance, and adeovir 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

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**PO - 041**

Outcome of 3-year Consolidation Therapy Following Virological Response in HBeAg-negative Chronic Hepatitis B Patients Treated with Nucleos(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 entecavir 0.5mg (42.6%), lamivudine (25.9%), lamivudine with adeovir (16.7%), adeovir (9.3%), clevudine (3.7%), or telbivudine (1.9%). Median follow-up time 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

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**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 ≥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 patients with and without 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 patients 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

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**PO - 043**

Outcome of 3-year Consolidation Therapy Following HBeAg Loss in HBeAg-positive Chronic Hepatitis B Patients Treated with Nucleos(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 HBsAg 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 HBsAg loss, and underwent 3-year consolidation therapy before stopping the treatment. Consolidation therapy was defined as NA treatment which was sustained after the first HBsAg 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 entecavir 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
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

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**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 ultrasoundography (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 3 days after admission due to acute hepatic failure and 12 weeks 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 (AUCROC) was 0.787 for 12 weeks mortality. The sensitivity, specificity, positive predictive value, negative predictive value for 12 weeks 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 (AUCROC) was 0.787 for 12 weeks mortality. The sensitivity, specificity, positive predictive value, negative predictive value for 12 weeks 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 (AUCROC) was 0.787 for 12 weeks mortality. The sensitivity, specificity, positive predictive value, negative predictive value for 12 weeks mortality was primary outcome.
sec for 12 weeks mortality was 0.645 (Confidence Interval, 0.440 - 0.948).

Conclusions: HVAT using a microbubble CEUS could be a 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 colon 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 colon 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 esophagastroduodenoscopic 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±9.1 months. 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±1.2 months vs. 30.7±0.4 months, p=0.013). In subgroup of 558 patients with prior decompensation, survival of ACLF group was shorter than no ACLF group (23.3±1.7 months vs. 29.1±0.6 months, 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±2.6 months vs. 23.6±1.3 months, 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
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% O2 and 5% CO2, at 37 °C) and hypoxic (1% O2, 5% CO2, and 94% N2, at 37 °C) 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

Secreted Tenascin C from Activated Hepatic Stellate Cells Promotes Epithelial-mesenchymal Transition in Hepatic Cancer Cell

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Aims: Hepatostellate 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. Tenasin 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 decreased 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: Tenasin C, Hepatic stellate cell, Hepatocellular carcinoma, Epithelial-mesenchymal transition

Ursodeoxycholic Acid-induced Apoptosis of Hepatocellular Carcinoma Cells Is Mediated by the Activation of Extrinsic
Synergistic Effect of CD44 and TGF-β1 during Epithelial-mesenchymal Transition through AKT/GSK3β/γ-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-β1) 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 the 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/γ-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/γ-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/γ-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/GSK3β/γ-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-β1, HCC

Integrative Transcriptome and Metabolome Analysis of Hepatic Cancer Stem Cells

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Background: Liver cancer stem cells (LSCs) 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 LSCs 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 LSCs 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 NRASQ61L, 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 KRAS4BG12V 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

**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 2cm, 10% (11/111) based on more than 3cm. Missing case was 12 patients in surveillance by one operator group (71 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 2cm, 10% (11/111) based on more than 3cm. Missing rate was 33.8% (24/71) based on more than 2cm, 10% (11/111) based on more than 3cm.

**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,
The Liver Week 2016

**Figure 1.**

<table>
<thead>
<tr>
<th>Size</th>
<th>One operator</th>
<th>Multi operator</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 cm</td>
<td>12/71 (16%)</td>
<td>40/111 (36%)</td>
<td>52/182 (29%)</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>14/40 (35%)</td>
<td></td>
<td>66/111 (35%)</td>
</tr>
<tr>
<td>&gt; 3 cm</td>
<td>22/111 (20%)</td>
<td></td>
<td>44/111 (40%)</td>
</tr>
</tbody>
</table>

**Missing rate**

- One operator: 33.3% (4/12)
- Multi operator: 0% (0/14)
- Total: 24% (22/92)

**Figure 2.**

**The cause of missing diagnosis in less than 2cm HCC**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Missing case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echogenicity</td>
<td></td>
</tr>
<tr>
<td>S7/8</td>
<td>4</td>
</tr>
<tr>
<td>S2/3</td>
<td>3</td>
</tr>
<tr>
<td>S4</td>
<td>2</td>
</tr>
<tr>
<td>S6</td>
<td>2</td>
</tr>
<tr>
<td>S1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12/71 Patients</td>
</tr>
</tbody>
</table>

**Figure 3.**

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

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**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 HBsAg 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

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**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-
Distant Metastasis and Liver Function Substaging of Barcelona Clinic Liver Cancer Stage C Hepato- cellular 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%. 156 patients with stage BCLC-C were classified as mlJCC stage III/IV/VA/VI in 1.9/15.4/50/29.5/3.2%, and were classified as AJCC TNM stage III/IV/VA/VIIC/VII in 1.9/25.6/63.5/3/2.7/1/9/1/90.6%. First-line treatment method was classified as supportive care/resection/radiofrequency ablation (RFA)/transarterial chemoembolization (TACE)/TACE+RT/hepatic arterial chemoembolization (HAI)/Sorafenib/radiation therapy(RT)/sorafenib+RT/follow up loss in 12.5/11.3/65.9/4.1/9/1/3/0.6/0.6/8.8%.

**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

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**PO - 059**

Substaging of Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma by Tumor Size, Major Portal Vein Invasion, Distant Metastasis and Liver Function

Dongwon Lee, Hyung Joon Yim, Seong Kyun Na, Seung Young Kim, Sang Jin Suh, Jong Jin Hyun, Sang Woo Jung, Young Kil Jung, Ja Seol Koo, Ji Hoon Kim, Yeon Seok Seo, Jong Eun Yeon, Sang Woo Lee, Kwan Soo Byun, Soon Ho Um

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2. Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea
3. Department of Internal Medicine, Korea University Anam Hospital, Seoul, Korea

**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=0.004) 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 sub staging 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

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**PO - 060**

Sub-classification of Advanced Stage Hepatocellular Carcinoma based on a Real-life Cohort

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

**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

<table>
<thead>
<tr>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score 5-6</td>
<td>0</td>
</tr>
<tr>
<td>7-9</td>
<td>7</td>
</tr>
<tr>
<td>Log(AFP) 0-3</td>
<td>0</td>
</tr>
<tr>
<td>3-6</td>
<td>3</td>
</tr>
<tr>
<td>6-9</td>
<td>6</td>
</tr>
<tr>
<td>9-10</td>
<td>10</td>
</tr>
<tr>
<td>Tumor type Nodular</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse or infiltrative</td>
<td>5</td>
</tr>
<tr>
<td>Portal vein invasion Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Extrahepatic metastasis Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
<tr>
<td>Total points</td>
<td>24</td>
</tr>
</tbody>
</table>

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 carcinoma, 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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1Center for Liver Cancer, 2Biometric Research Branch, National Cancer Center, Goyang, Korea

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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Park, Seong Gyu Hwang, Kyu Sung Rim
Department of Gastroenterology, CHA Bundang Medical Center, CHA University

**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 at L3 level of computed tomography scan in 132 patients newly diagnosed with hepatocellular carcinoma (HCC) was defined as L3 skeletal muscle index of ≥ 52.4 cm²/m² for male and ≤ 38.5 cm²/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=0.012), 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, 6.5 vs. 2.07, P=0.001) 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

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**PO - 064**

Plasma MicroRNA-21, 26a, and 29a as a Predictive Marker for Treatment Response Following Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

Soon Sun Kim1, Ji Sun Nam2, Hyo Jung Cho3, Ji-Hyun Kim1, Han Gyew Kim1, Ga Ram Lee1, Je Hwan Won2, Jin Woo Kim2, Sung Won Cho1, Jae Youn Cheong1
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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-
significant 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 carcinoma, MicroRNA-21, MicroRNA-26a, MicroRNA-29a, Survival, Treatment failure

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**PO - 066**

The Comparison Study between Contrast-enhanced Ultrasoundography and Dynamic Contrast-enhanced Computed Tomography to Assess the Response of Transarterial Chemoembolization for Hepatocellular Carcinoma: A Prospective Pilot Study

Yong Kwon Kim1, Min Young Baek1, Jae Young Jang1*, Soung Won Jeong1, Sae Hwan Lee2, Sang Gyu Kim3, Sang-Woo Cha4, Young Seok Kim5, Young Deok Cho2, Hong Soo Kim2, Boo Sung Kim2

1. Department of Internal Medicine, College of Medicine, Soonchunhyang University, Seoul, South Korea, 2. Department of Gastroenterology, Department of Surgery, Inje University College of Medicine, Ilsan, South Korea, 3. Department of Internal Medicine, College of Medicine, Soonchunhyang University, Cheonan, South Korea, 4. Department of Internal Medicine, College of Medicine, Soonchunhyang University, Bucheon, South Korea

**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:** 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 (κ=0.791, p=0.025) and substantial agreement between MDCT and hepatic arteriography (κ=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

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**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:** Contrast-enhanced ultrasonography (CEUS) is commonly used to evaluate the residual tumor of HCC after treatment with TACE by using hepatic arteriography as a golden standard.
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, Gadoteric acid-enhanced MRI
Does Transarterial Chemoembolization prior to Surgical Resection Improve Clinical Outcomes in Resectable Hepatocellular Carcinoma?

Hye Ji Kim1, Jung Hyun Kwon1, Young Woon Kim1, Soon Woo Nam1, Jong-Yul Lee2, Hyun Suk Jung2, Yu Ri Shin2, Young Chul Yoon3, Jun Suh Lee2, Sung Won Lee1, Hae Lim Lee1

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Background: The efficacy of transarterial chemoembolization (TACE) performed prior to surgical resection in patients with resectable hepatocellular carcinoma (HCC) is still a matter of debate. This study aimed to assess the impact of preoperative TACE in patients with resectable HCC.

Methods: A total of 117 consecutive HCC patients who received hepatectomy/radiofrequency ablation in the Barcelona Clinic Liver Cancer stage O/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) and validation set (n=491). 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=867) on 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

Prognosis of Early Stage Hepatocellular Carcinoma Showing Complete Response after First Transarterial Chemoembolization: A Role of Scheduled Second TACE

Jung Hee Kim1, Dong Hyun Sinn1, Sung Wook Shin2, Sung Ki Cho2, Wonseok Kang3, Geum-Youn Gwak4, Joon Hyosek Lee5, Kwang Cheol Koh6, Seung Woon Paik2, Moon Seok Choi1

1Department of Medicine, 2Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

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

Moon Won Lee1, Hyun Young Woo1, Jeong Heo1, Won Lim1, Young Mi Hong2, Ki Tae Yoon1, Mong Cho1, Won Taek Kim1

1Department of Internal Medicine, College of Medicine, Pusan National University, Busan, Korea, 2Department of Radiation Oncology, College of Medicine, Pusan National University, Busan, Korea

**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%).

**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

Baek Gyu Jun1, Young Don Kim4, Gab Jin Cheon1, Sae Hwan Lee2, Hong Soo Kim1, Sang Gyune Kim1, Young Seok Kim1, Boo Sung Kim1, Song Won Jeong1, Jae Young Jang1

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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 recovery rate of RILD (P<0.01) increases, and the recovery rate of RILD (P<0.01) increases.

**Table 3. Multivariate analysis of parameters associated with risk of RILD**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/CP score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12.214</td>
<td>0.431</td>
<td>0.020</td>
</tr>
<tr>
<td>6</td>
<td>28.590</td>
<td>1.371</td>
<td>0.020</td>
</tr>
<tr>
<td>7</td>
<td>228.000</td>
<td>3.377</td>
<td>0.020</td>
</tr>
<tr>
<td>8</td>
<td>10.949</td>
<td>10.391</td>
<td>0.020</td>
</tr>
<tr>
<td>PVTT score</td>
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<td></td>
<td></td>
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<tr>
<td>2</td>
<td>2.465</td>
<td>0.406</td>
<td>0.127</td>
</tr>
<tr>
<td>6</td>
<td>1.000</td>
<td>1.000</td>
<td>0.687</td>
</tr>
<tr>
<td>Total liver volume</td>
<td></td>
<td></td>
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<tr>
<td>0.999</td>
<td>1.000</td>
<td>1.000</td>
<td>0.687</td>
</tr>
</tbody>
</table>

![Figure 1. Rate of RILD and recovery rate RILD Linear by linear association model.](image-url)
Clinical Outcomes of Patients with a Single Hepatocellular Carcinoma Less Than 5 cm Treated with Transarterial Chemoembolization

Min Young Bae1, Soyang Won Jeong2, Jae Young Jang3, Jae Hwan Lee4, Sang Gyune Kim5, Sang-Woo Cha1, Young Seok Kim6, Young Deok Cho7, Hong Soo Kim5, Boo Sung Kim1

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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 1.9 cm (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 were predictive factors for OS.

Conclusions: Complete local tumor control by combination of TACE and 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

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**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 sorafenib in case of tumor progression after TAC with single agent, doxorubicin (TAC-DOX). As a novel therapeutic strategy, the efficiency 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 5FU (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=3), 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

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**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 cholangiocarcinoma), 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 portal-hepatico-portal 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.

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**PO - 078**

Can Sorafenib Increase Survival for Recurrent Hepatocellular Carcinoma after Liver Transplantation?

Seong Hee Kang1, Eun Ju Cho1, Joon Yeul Nam1, Young Chang2, Hyewon Cho3, Young Youn Cho1, Jeong-Hoon Lee4, Su Jung Yu4, Yoon Jun Kim4, Nam-Joon Yi2, Kwang-Woong Lee5, Kyung-Suk Suh6, Jung-Hwan Yoon1

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**Purpose:** Sorafenib is an effective treatment option for patients with advanced hepatocellular carcinoma (HCC). However, there are a few limited options including sorafenib in case of tumor progression after TAC-DOX. As a novel therapeutic strategy, the efficacy of transcatheter arterial chemoembolization (TACE) has been recognized as an effective therapy for advanced hepatocellular carcinoma (HCC). However, there are a few limited options including sorafenib in case of tumor progression after TAC-DOX. As a novel therapeutic strategy, the efficacy of transcatheter arterial embolization, Doxorubicin, Epirubicin
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, Sorafenib, Cytotoxic chemotherapy

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 sorafenib 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
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
Role of Endoscopic Biliary Drainage in Advanced Hepatocellular Carcinoma with Jaundice

Hyun Young Woo, Sung Yong Han, Jeong Heo, Dong Uk Kim, Dong Hoon Baek, Won Lim, Ki Tae Yoon, Young Mi Hong, Mong Cho

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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 21.7% (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 prevalence of intrahepatic bile duct dilatation was significantly associated with complete resolution of jaundice in multivariate analysis (p<0.001). In overall, 90 days survival rate was 24.2% and median survival was 74.3% (29/39) median 88 days (range, 5-399 days) after resolution.

Discussion: The presence of intrahepatic bile duct dilatation was significantly associated with complete resolution of jaundice in multivariate analysis (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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 70</th>
</tr>
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<tr>
<td>Sex (male), n (%)</td>
<td>61(87.1)</td>
</tr>
<tr>
<td>Age, years</td>
<td>62.3±9.7</td>
</tr>
<tr>
<td>Etiology (A/B/C), n (%)</td>
<td>10/44/16 (14.3/62.8/22.9)</td>
</tr>
<tr>
<td>BCLC (A/B/C), n (%)</td>
<td>0/10/60 (0/14.3/85.7)</td>
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<td>Okuda (I/II/III), n (%)</td>
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<td>Tumor volume (&gt;50%), n (%)</td>
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<td>PVT, n (%)</td>
<td>47 (67.1)</td>
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<td>Metastasis, n (%)</td>
<td>18 (25.7)</td>
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<td>Ascites, n (%)</td>
<td>37 (52.9)</td>
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<td>Encephalopathy, n (%)</td>
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<td>Prior HCC treatment history, n (%)</td>
<td>52 (74.3)</td>
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<tr>
<td>Intrahepatic bile duct dilatation, n (%)</td>
<td>35 (50)</td>
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<td>Location (Total/Right/Left/Segment 4)</td>
<td>19/19/5/12 (22.9/22.9/7.1/17.1)</td>
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<td>Child (A/B/C), n (%)</td>
<td>2/46/22 (2.9/65.7/31.4)</td>
</tr>
<tr>
<td>Aspartate transaminase, IU/L</td>
<td>228.8±200.0</td>
</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>9.13±5.83</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.87±0.36</td>
</tr>
<tr>
<td>Creactive protein, mg/dl</td>
<td>4.0±3.1</td>
</tr>
<tr>
<td>Prothrombin time (INR)</td>
<td>1.36±0.21</td>
</tr>
</tbody>
</table>

Continuous variable, mean±standard deviation
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 were enrolled. 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.

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

Outcomes of Living and Deceased Donor Liver Transplant Recipients according to the MELD Score

Jae Geun Lee1, Jae Jun Lee1, Jung Hyun Kwon1, Jung Chul Yoon1, Yu Ri Shin1, Hye Ji Kim1, Eun Chung1, Young Woon Kim1, Jeong Won Jang1, Soon Woo Nam1, Nam Il Han1, Kyu Won Chung2

1Department of Internal Medicine, 2Department of General Surgery, 3Department of Radiology, The Catholic University of Korea, Seoul, Korea

Aims: Living donor liver transplantation (LDLT) has developed as an alternative to deceased 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) LDLT and DDLT groups, patients with high MELD score showed significantly lower graft survival than patients with low MELD score.

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 showed 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 MELD are risk factor for graft mortality in overall patients. However, HCV and high MELD
Transplantation versus Hepatectomy for Hepatocellular Carcinoma 2 cm or Less Than 2 cm

Xu-Guang Hu, Hee-Jung Wang, Bong-Wan Kim, Mao Wei, Sung Yeon Hong

Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Ajou University School of Medicine, Suwon, Korea

Aims: Surgical resection has been the treatment of choice for early stage Hepatocellular carcinoma (HCC), and the overall survival was satisfied. However, the postoperative recurrence rate is a significant problem. The shortage of organ donors has led to a restricted indication for orthotopic liver transplantation for HCC. The aim of this study was to analyze the results of surgical treatment for 2 cm or less than 2 cm 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 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 retrospectively 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 2 cm HCC.

Keywords: Hepatocellular carcinoma, Transplantation, Hepatectomy

HSV after LDLT

Abylaikhan Sharmenov, Gani Kuttymuratov, Tokan Sultnaliyev, Mukazhanov Adilbek, Zhelisembayev Asan, Yermakhan Assylkhanuly, Melis Asylkhanova, Said Abdulgafarov

JSC "National Research Center for Oncology and Transplantology", Department of Transplantology, Department of Vascular Surgery, Astana, Kazakhstan

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 Prednison. 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) 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) No22, 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 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, Famcylovir 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

LDLT for Non-cirrhotic Portal Hypertension from Cavernous Transformation of Portal Vein - A Case Report

Sung Yeon Hong, In-Gyu Kim, Xu-Guang Hu, Hee-Jung Wang, Bong-Wan Kim

Division of Liver Transplantation and Hepatobiliary Surgery, Department of Surgery, Ajou University School of Medicine, Suwon, Korea

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 successfully performed. The thick paracholedochal vein was an alternative option for adequate portal inflow. We anastomosed it with donor common bile duct and paracholedochal collateral vein. One thick paracholedochal vein of them looked like an candidate of alternative 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. Postoperative 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, on blook 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

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**PO - 089**

Changes in T Cells in Peripheral Blood after Adult Liver Transplantation

Jong Man Kim, Jisoo Lee, Kyung-Sik Kim, Nuri Lee, Chan-Woo Cho, Gyu-Seong Choi, ChoonHyuck David Kwon, Jae-Won Joh

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

**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 V61/V62 ratio in the LDLT group was higher than in the DDLT group (P=0.045). Comparison between LDLT and DDLT groups revealed that CD4+ T cells, CD8+ T cells, CD4/CD8, V61 cells, V62 cells, and V61 to V62 cells did not change significantly over time. The V61/V62 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 V62 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. V62γδ T cells are closely associated with CMV infection and graft failure.

**Keywords:** Liver transplantation, T lymphocyte, Cytomegalovirus infection, Graft failure, Biopsy-proven acute rejection

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**PO - 090**

Relevance of the Tumor Site and Node Metastasis in Patients with Intrahepatic Cholangiocarcinoma

Woohyung Lee, Jae Yool Jang, Soon-Chan Hong, Chi-Young Jeong

Department of Surgery, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine and 79 Gangnam-ro, Jinju, 52727 Republic of Korea

**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 perihilar (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
Conclusions: Variate regression analysis were found to be independent factors for overall survival in multi-
ease free survival for the HCC (less than 5 cm) patient after an independent and significant predictor for overall survival and dis-
regression analysis. And high SUV (3.75) was 4.75) and large tumor size (3.75) was
were 94.8%, 90.3%, 90.3% and 81.6%, 64.4%, 56.3%, 1, 3, 5 years cumulative overall survival rates and disease free survival
The median follow-up period was 32.5 months (Range, 82). The
peritoneal 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 sig-
nificance 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 dis-
section with hepatectomy.

Keywords: Intrahepatic cholangiocarcinoma, Liver resection, Oncologic
outcome, Tumor site

The Liver Week 2016

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)

In-Gyu Kim, Xu-Guang Hu, Hee-Jung Wang, Bong-Wan Kim,
Sung Yeon Hong

Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Ajou University School of Medicine, Korea

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 5 cm) 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 multi-
variate regression analysis.

Conclusions: The high SUV (>4.75) on 18F-FDG-PET/CT imaging was an independent and significant predictor for overall survival and dis-
ease free survival for the HCC (less than 5 cm) patient after hepatectomy.

Keywords: Hepatocellular carcinoma, PET CT, Survival

PO - 092

Case-control Study of Pure Laparoscopic Hemihepatectomy vs. Open Left Hemihepatectomy for Hepatocellular Carcinoma

Hwui-Dong Cho, Ki-Hun Kim*, Shin Hwang, Chul-Soo Ahn,
Duk-Bok Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung,
Gil-Chun Park, Sung-Gyu Lee

Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Ulsan University and Asan Medical Center, Korea

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 peripro-
avative 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 post-
operative complication which was mild ileus in the LLH group.

Conclusion: Pure laparoscopic left hemihepatectomy for hep-
ato cellular carcinoma was safe and feasible procedure for selected patients.

PO - 093

The Role of Curative Intent Surgical Resection for the Recurrent HCC

Seung Hwan Song1,2, Jee Youn Lee1,2, Su-kyung Kwon1,2, Juhan Lee1,2,
Jae Geun Lee1,2, Dai Hoon Han1,2, Gi Hong Choi1,2, Jin Sub Choi1,2,
Myoung Soo Kim1,2, Soon Il Kim1,2, Dong Jin Joo1,2

1Department of Surgery and 2The Research Institute for Transplantation, Yonsei University College of Medicine, Seoul, Korea

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 Hapatocel-
lar carcinoma (HCC) after liver transplantation remains one of the major causes to graft failure and patient death. Because HCC re-
currence 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 trans-
plantation 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 out-
comes of the recurred patients according to the therapeutic approaches.
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

Table 1. Patient and tumor data

<table>
<thead>
<tr>
<th></th>
<th>HCC recur (n=37)</th>
<th>No HCC recur (n=192)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>60.9 ± 6.17</td>
<td>54.4 ± 6.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex (M/F) %</td>
<td>32/5</td>
<td>156/36</td>
<td>0.447</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td></td>
<td></td>
<td>0.357</td>
</tr>
<tr>
<td>HBV</td>
<td>33(86.8%)</td>
<td>158(82.7%)</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>3(7.9%)</td>
<td>18(9.4%)</td>
<td></td>
</tr>
<tr>
<td>HBV + HCV</td>
<td>1(2.6%)</td>
<td>1(0.5%)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>0(0%)</td>
<td>0(0.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0(0%)</td>
<td>5(2.6%)</td>
<td></td>
</tr>
<tr>
<td>AFP</td>
<td>292.8 ± 622.2</td>
<td>50.4 ± 232.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Criteria</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Milan</td>
<td>19(51.4%)</td>
<td>158(82.3%)</td>
<td></td>
</tr>
<tr>
<td>UCSF</td>
<td>6(16.2%)</td>
<td>9(4.7%)</td>
<td></td>
</tr>
<tr>
<td>≥UCSF</td>
<td>12(32.4%)</td>
<td>28(13.1%)</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.001

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

PE-001—PE-004  Alcoholic Liver Disease
PE-005—PE-009  Cell Biology / Molecular Biology
PE-010         Drug and Toxic Injury
PE-011—PE-016  Genetic
PE-017—PE-020  HBV, Basic
PE-021—PE-036  HBV, Clinical
PE-037—PE-053  HCV, Clinical
PE-054—PE-059  Liver Cancer, Basic
PE-060—PE-095  Liver Cancer, Clinical
PE-096—PE-099  Liver Cirrhosis, Portal Hypertension with Cx. Basic
PE-100—PE-107  Liver Cirrhosis, Portal Hypertension with Cx. Clinical
PE-108—PE-115  Liver Failure, Acute
PE-116—PE-142  Liver Transplantation
PE-143—PE-145  Liver, Infectious Disease
PE-146—PE-149  NAFLD, Basic
PE-150—PE-153  NAFLD, Clinical
PE-154—PE-160  Other Surgical Issues
PE-161—PE-171  Others
Alcoholic Liver Disease

**PE - 001**

Outcome of Deceased Donor Liver Transplantation for Alcoholic Liver Disease

Suk Kyun Hong, Nam-Joon Yi, Kyung Chul Yoon, Hyo-Sin Kim, Hyeyoung Kim, Kwang-woong Lee, Kyung-Suk Suh

Department of Surgery, Seoul National University Hospital

**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 7 day GGT was the only predictive factors associated with death or liver transplantation in ALD group. 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

Yermalhan Assyldihanuly, Gani Kuttymuratov, Baldyty Zharikmbekov, Mels Asykbayev, Saithkarim Abdugafarov

JSC “National Research Center for Oncology and Transplantology”

**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 win-

dow 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 to 3 recipients 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 orthotopic liver transplantation (OLT).

**Results:** Indications for OLT was Child-Turcotte-Pugh score >7 with single episode of spontaneous bacterial peritonitis and an 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. Surveys 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 7 days, and early change bilirubin levels (ECBL) at 7 days were predictive factors by univariate analysis. In multivariate analysis, female (HR, 3.023; 95% CI, 1.169-7.347, p=0.024), absence of ECBL at 7 days (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

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**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- iNKT cell in patients with SAH were lower compared to those of healthy controls. There were two types of changing pattern of peripheral CD1d+ iNKT cell in patients with SAH. First is increasing pattern of peripheral CD1d+ iNKT cell at W1 compared to W0 (SAH 1 group). The second is decreasing pattern of peripheral CD1d+ iNKT 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+ iNKT cell can be used as biomarker for steroid treatment of patients with SAH patients.

**Keywords:** Severe alcoholic hepatitis, NKT cell

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**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 absence (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-type 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

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**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 ATBF1 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 trans-differentiation 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 an 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. Intracellular 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-treatment of LX-2 with Nifedipine (an L-type calcium channel blocker) suppressed CTGF induction by TGF-b in dose-dependent manner, while PL64176 (L-type calcium channel activator) increased CTGF expression without TGF-b. The CTGF up-regulations by TGF-b, A23187, and PL64176 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 is necessary to overcome such limitation. Here, we suggest 3-dimensional (3D) bioprinting technique as one of the most promising techniques.

Methods: To isolate mouse primary hepatocytes, collagenase was injected into 4-6 weeks mouse liver. Isolated hepatocytes were stained albumin, HNF4alpha and Hepat1 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 by 2D and 3D. Sandwich 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. Culture 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 collagenase methodology isolated primary hepatocytes (8×10^7 cells/mice). Our methods could isolate hepatocytes with 70–80% viability. These hepatocytes were immuno-stained and qRT-PCR with 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 (25×25 mm) with primary hepatocytes using 3D bioprinter. Surprisingly, the cells were 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

ZLITHAMACR
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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.

Keywords: Zizania latifolia, Wild rice, Toxic hepatitis, Myopathy
The Major Changes of Gilbert’s Syndrome and UGT1A1 Gene Abnormalities in Mongolians Are Western Type

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Aims: Hereditary abnormalities of uridinephosphogluconate-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 tested for bloodchemistries, 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)3TAA (6) or A(TA)2TAA (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 67 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

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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, PCDH811, 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 PCDH811 were little expressed in both tumor and non-tumor, which is not consistent with our previous result. In apart, GSPN2 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 size 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.
Aims: Hereditary abnormalities of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene is associated with unconjugated hyperbilirubinemia 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 homozygous 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

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±0.16 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±0.45 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
Whole-genome Sequencing of Two Liver Tumors from One Patient

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Aims: There is widely known that numerous genomic variance involved in carcinogenesis. Recent advances in technology make it possible to approach 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

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-feto-protein in Cytokine-dependent Manner

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Aims: Alpha-feto-protein (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: Transfection 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 indirectly act on the promoter, Treatment with inflammatory cytokines (TNAs and IFN) additionally increase 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

**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 and CTLA-4 on CD4+ T cell and CTLA-4 on CD8+ T cell. 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. 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

**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-
HBsAg (TDF) in 15 patients (14.3%). During 3 years treatment, 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 HBsAg 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, HBsAg 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 HBsAg negative patients.

Keywords: HBsAg, Chronic hepatitis B, Antiviral agent

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 two groups retrospectively.

Results: Presence of jaundice and hepatitis B envelope 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 log10 IU/mL vs. 6.7 log10 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 envelope 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 HBeAg reduction were significantly higher in the AHB group compared to the CHB-AE group.

Keywords: Acute hepatitis B, Chronic hepatitis B, Hepatitis B sensory complex
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 subgroup 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
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 aminotransferase were not significantly different between two groups (P=0.210 by log-rank test). 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 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.

**Keywords:** Tenofovir, Lamivudine resistance, Adefovir resistance, Chronic hepatitis B

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**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-naive 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 10E8 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-naive CHB patients exhibiting a PVR to TDF therapy.

**Methods:** This retrospective study included 139 treatment-naive 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-naive 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:** This retrospective study included 139 treatment-naive 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-naive CHB patients exhibiting a PVR to TDF therapy.

**Keywords:** Chronic hepatitis B, Tenofovir, Partial virologic response
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 HBsAg positive. Mean baseline HBsAg level and HBV DNA level were 3.47 ± 0.1 log10IU/mL and 6.37 ± 1.36 log10IU/mL, respectively. In HBsAg 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 HBsAg 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 HBsAg 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 seroconversion 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 hepatocellular carcinoma (HCC) can still develop in chronic hepatitis B patients after hepatitis 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 large 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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www.theliverweek.org 139
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-naive patients who started either ETV or TDF by randomization manner between January 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-naive 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

Incidence, Predictors and Clinical Course of Partial Virologic Response to Tenofovir in Treatment-naive 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-naive 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-naive patients with chronic hepatitis B.

Methods: Between November 2012 and December 2014, total of 319 treatment-naive patients with CHB achieved a 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 48 weeks of therapy, 119 (22.9%) patients achieved VR and 45 (37.8%) patients achieved VR among PVR patients, following 96 weeks of therapy. HBsAg positive patients achieved more PVR (119, 43.59%) compared with HBsAg 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 HBsAg positivity (54.6%, P=0.001) and less HBsAg 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 24 weeks of TDF therapy, 400 patients (77%) achieved VR. 119 (22.9%) patients showed PVR after 48 weeks 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 patients without PVR and more patients with HBeAg showed PVR. Patients with PVR achieved less HBsAg 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

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, HBsAg 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 HBV DNA is 6.2±1.30, 57.6% of them had HBsAg 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 HBsAg 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 anti-diabetic 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
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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

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**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-naive 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-naive, 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-transplantation

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**PE - 039**

Ledipasvir/Sofosbuvir for 8 Weeks in Genotype 1 Treatment-naive Non-cirrhotic Patients with HCV RNA < 6 Million IU/mL: Phase-3 and Real World

Peter Buggisch1, Jorg Peterson1, Stefan Mauss2, Kris Kowdley3, Micheal Curry4, Peter Ruane5, Dani Aln, Naqoy Tsai1, Yoori Lee7, Edward Eggleton8, Madsy Natha9, Bruce Kreuter9, Diana Brainard1, Jin Youn10, Patrick Inglim11

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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 ICON-3 (treatment-naive (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
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 that 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 RME 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 of anti-HCV SCO ratio for predicting HCV viremia, and for discriminat-

**Poster Exhibition**

**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 (SCO) 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 SCO 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% (20362) of the patients showed false-positive antibody results. There were significant differences in serum ALT level, anti-HCV SCO ratio and RIBA results (viremia vs. non-viremia, TP vs. FP). Using ROC curves, the optimal cutoff values of anti-HCV SCO 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 SCO ratio were 98.0%, 88.4%, 91.6% and 97.2%, respectively. Those for TP at 6 of anti-HCV SCO ratio were 97.0%, 99.0%, 99.5% and 83.4%, respectively. Using the level of 6 of anti-HCV SCO 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 SCO 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 & laboratory evaluations.

**Results:** 5433 patients enrolled in the SVR registry with a median
**PE - 042**

Epidemiology and Genotype Distribution of HCV in Mongolia

Sosorbaram Ariunaa, D.Munkh-Orshikh, Ch.Bolormaa, B.Gansai-Epidemiology and Genotype Distribution of HCV in Mongolia

<table>
<thead>
<tr>
<th>Age (years SD)</th>
<th>SVR Registry N=5433</th>
<th>HCV Genotype DAA SVR Registry N=536</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>3405 (62.7)</td>
<td>417 (77.8)</td>
</tr>
<tr>
<td>Cirrhosis, n (%)</td>
<td>1088 (20.0)</td>
<td>117 (21.8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Caucasian</td>
<td>African Descent</td>
</tr>
<tr>
<td>IL28B Genotype, n (%)</td>
<td>CC 1608 (29.6)</td>
<td>CT 2826 (52.0)</td>
</tr>
<tr>
<td>HCV Genotype, n (%)</td>
<td>1 3618 (66.6)</td>
<td>2 535 (9.8)</td>
</tr>
<tr>
<td></td>
<td>333 (62.1)</td>
<td>27 (5.0)</td>
</tr>
</tbody>
</table>

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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5. Mongolian Association for the Study of Liver Diseases

**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 advanced 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%.

**Keywords**: HCV, Treatment, Mongolia.
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

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**PE - 044**

The Efficacy and Safety of Daclatasvir and Asunaprevir for Hepatitis C Virus Genotype 1 Infection in Old Age Patients with Compensated Cirrhosis

Hee Chul Nam1, Hyun Yang2, Hae Lim Lee2, Myeong Jun Song2*

Department of Internal Medicine1, The Armed Forces Hongcheon Hospital, Hongcheon, Korea, Division of Hepatology2, Department of Internal Medicine, College of Medicine, The Catholic University of Korea

**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

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**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

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**PE - 046**

Nationwide Seroepidemiology of Hepatitis C Virus Infection in South Korea, Data from National Health and Nutrition Examination Survey 2012–2014

www.theliverweek.org 145
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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 health 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 distribution compared with previous reports mostly based on data from health check examinees.

**Keywords:** Hepatitis C, Prevalence, Korea, General Population

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**Table 1. Treatment-emergent AEs and laboratory abnormalities**

<table>
<thead>
<tr>
<th>With cirrhosis n=521</th>
<th>Without cirrhosis n=521</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE*, n (%)</td>
<td>1 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>AEs leading to study drug discontinuation, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs in ≥20% of either patient group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11 (18)</td>
<td>107 (21)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (21)</td>
<td>98 (19)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (20)</td>
<td>38 (7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (10)</td>
<td>42 (8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (10)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>6 (10)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (10)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Post-baseline laboratory abnormalities, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 (&lt;10.0 g/dL)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 (≥10.0 g/dL)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 (≥20 x UUL)</td>
<td>1 (2)*</td>
<td>1 (0.2)*</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 (≥10 x UUL)</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

* — Serious AEs: Arthritis, hypothyroidism, dermatologic conditions, dyspepsia, desquamative gingivitis, nasopharyngitis, pericarditis, fracture of ribs.

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**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-II; 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.

**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%). SVR12 rates 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.

**Keywords:** HCV GT1b, Ombitasvir, Paritaprevir/Ritonavir, Dasabuvir

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ONXY-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 southern Asian populations. The ONXY-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 ONXY-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

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

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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### Table 1

<table>
<thead>
<tr>
<th>SVR 12 (%)</th>
<th>Post-transplantation with F8-13</th>
<th>Pre or post-transplantation with decompensated cirrhosis (CPT B or C)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 weeks</td>
<td>24 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patients with NS5A RAVs</td>
<td>23/23 (100%)</td>
<td>21/21 (100%)</td>
<td>19/24 (79%)</td>
</tr>
<tr>
<td>Patients with no NS5A RAVs</td>
<td>135/136 (99%)</td>
<td>132/132 (100%)</td>
<td>108/112 (94.6%)</td>
</tr>
</tbody>
</table>

#### GT 4 HCV-infected patients

<table>
<thead>
<tr>
<th></th>
<th>Patients with NS5A RAVs</th>
<th>Patients with no NS5A RAVs</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/9 (100%)</td>
<td>6/6 (100%)</td>
<td>2/2 (100%)</td>
<td>5/5 (100%)</td>
</tr>
</tbody>
</table>

#### GT 1 HCV-infected patients

| 1/1 (100%) | 4/4 (100%) | 1/1 (100%) | 10/10 (100%) |

#### 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 42, 28, 30, 31, 58, and 93 were enriched or emerged in 20/22 (91%) GT1 and 1/3 GT 4 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 transplantation 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

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### 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

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**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 impact 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=0.013) and for the RAN rs14035 CT compared with the CC genotype (hazard ratio [HR]: 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

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**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=8.88, 95% confidence interval [CI]=1.88-41.750, 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

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**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 c-Myc 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-
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-jejunostomy 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% (FLV/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

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 SNPSstats 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

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

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**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 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. MAT1A/MAT2A switch has been severely 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 I 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 well 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**: Immunohistochemical 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

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**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 hemangioma 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**: 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 hemangioma sized 10 cm in diameter and tiny hemangiomas less than 1 cm 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 up to 16cm in diameter and newly appeared numerous hemangiomat-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
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 (1.0-202.90) 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 (NLCS) 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 NLCS 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 NLCS in Korea. Old age and presence of liver cirrhosis are associated with higher risk of HCC development.

**Keywords:** Hepatocellular carcinoma, Chronic hepatitis B, Screening
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**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. However, the incidence of HCV-related HCC was similar in the two countries; 519 and 570 per 100,000 patients and Taiwan, respectively. However, the incidence of HCV-related HCC to HBV-related HCC was 434 and 136 per 100,000 patients in Korea and Taiwan, respectively. The mortality rate due to HBV-related HCC was 1.97%. 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

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**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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**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/m²), normal
weight (18.5-22.9 kg/m²), overweight (23.0-24.9 kg/m²), and obesity (≥ 25.0 kg/m²).

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

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 the 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
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

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**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

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**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 (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

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**The Possibility of Radiotherapy for Downstaging before Living Donor Liver Transplantation for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis**

**PE - 071**
**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.

**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 morbidity 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).
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 χ² 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; χ² 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

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 fetoprotein. 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 (Histoacyrl) 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-histoacyrl 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

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% confidence 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 >12 kPa (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

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 first 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 compact 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

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
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 Sorafenib 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 capetibamine 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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www.theliverweek.org 161
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

Aims: Intraaductal papillary neoplasm 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 hepatojejunostomy. 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

A Randomized, Prospective, Comparative Study about Effects and Safety of Sorafenib vs. Hepatic Arterial Infusion Chemo therapy 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(PVT) were not acceptable and treatment modalities were limited. So, we compared effects and safety of sorafenib vs. hepatic arterial infusion chemo therapy(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
PE - 086

AssOCIATING 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 centralhepatectomy 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(LLS+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-
Sarcopenia May Be Associated with the Mortality in Patients with Hepatocellular Carcinoma

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**Aims:** Sarcopenia has been 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) vertebra 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). Sarcopenia 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 - 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 patients 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 bleeding ligation. Among the 112 patients treated with TAE, 44 underwent staged partial hepatectomy, 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 disease-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 (MR: 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 MIR+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% MR, and 49.0% MNR (P=0.815).
There were also no significant differences 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**

**Associating 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+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 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

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 (LLS+S1+RPS) was 589mL (395+16+178) at postoperative 8 days although biloma was identified at resection area. She recovered at postoperative 1 month.
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 according 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 ≤ 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 ≤ 200 and 58.6% in the cases with AFP>200 among the BCLC B or C patient (p=0.002). And 3 year disease free survival rate was 55.8% in the cases with AFP ≤ 200 and 28.0% in the cases with AFP>200 (p=0.005). According to the multivariate 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 summary, 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 modified as new data comes to light.
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 during 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 mean 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 values 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, with an APRI of 0.61 (range 0.4 - 1.69), APRI of 4.42±2.5 kPa (range 0.1 - 13.1), and APRI of 4.04±1.8 in G6. The degree of collagen stain (%) were 0.19±0.03 in G4, 0.22±0.04 in G1, 1.6±0.53 in G2, and 1.66±0.4 in G3. The degree was higher in G2 than in G1 (p=0.001). However, there was no difference between G2 and G3. The degrees of collagen stain (%) were 0.22±0.04 in G1, 1.6±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
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 definitive prognostic stratification of tumor recurrence and patient survival rates according to the tumor type (P<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](image1.png)

**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 esophagogastroscope 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.

**Keywords:** 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 transplantations, 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.

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

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 (Odds ratio 7.71, P<0.0001), and serum creatinine level (Odds 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 (Odds ratio 5.11, P=0.009), serum creatinine level (Odds ratio 1.73, P<0.036), Child-Pugh score (Odds ratio 2.26, P=0.001) and treatment failure (Odds 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

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 varical bleeding and investigated the prognosis of decompensated liver cirrhosis.

Methods: We prospectively enrolled 83 patients with decompensated liver cirrhosis including ascites or varical 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

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**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 laboratory 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 occurred. 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 aggrivated ascites.

**Conclusions:** PARTO is a technically successful and clinically safe and effective procedure for the treatment of GV.

**Keywords:** Gastric varix, Variceal bleeding, PARTO

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**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
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-hepatitis 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

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 antitumor 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 8 weeks of BALB/c nude mouse by intraperitoneal injection of CCl4 (tetra-chloride, 0.5 ml/kg mix with corn oil 1:3). After 24 hr CCl4 injection, GFP-iHep(G) and GFP-MEF(GM) were administered by intrasplenic injection. Serum and livers were collected at specified time points (0, 4, 24, 48, 72 hr post cell injection). Serum ALT and AST were measured by EUSA. Degree of liver injury is confirmed by Hematoxylin-Eosin (H&E) staining. Immunofluorescence (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 CC14-induced acute liver injury. Consistent with previous reports, serum ALT/AST levels were peaked at 24hr after CC14 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 up to 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 CC14 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, 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

**PE - 111**

**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 higher 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

Aibolat Smagulov, Doskali Marlen, Rysmakhanov Myltykbai, Taganova

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°C, 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 suspicous acute hepatitis and fatty changes of liver.

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 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°C, 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 suspicous 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/dl, 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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### PE - 114

**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 pre-eclampsia, 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 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

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### PE - 115

**Prevalence and Predictors of Thrombocytopenia in Advanced Liver Disease**

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1Ittefaq Hospital Medicine Ladoore-Pakistan, 2Mayo Hospital Medicine Lahore-Pakistan, 3Nishtar Medical College Hospital Medicine Lahore-Pakistan

**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 \(150,000/Ul\) 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

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### 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 graft versus host disease(GVHD) 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

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 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

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
De Novo Hepatitis B Virus Infection after Liver Transplantation in Hepatitis B Core-positive Recipients Using Hepatitis B Core-negative Grafts

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
Spleenic 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 after 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.


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

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**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
Abscess was drained 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:** 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 artery, Liver transplantation, Ascites

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**Immunosuppression after Liver Transplantation**

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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 discontinued steroid after 6-12 month after transplantations, depending on the etiology of liver cirrhosis. One patient finished receiving MMF 2 years after transplantation. Two patients (after living donor transplantation) received (and receive now) only Tacrolimus and had no rejection episodes. But they were appointed hormones for a week after transplantations. One patient had a conversion from Tacrolimus to Cyclosporine. She had hyperglycemia. After conversion glucose levels returned to normal.

**Conclusions:** Minimization of immunosuppression is a necessary goal for the transplant patients. Many immunosuppressive drugs have side effects, which lead to undesirable consequences or death. Immunosuppression minimization regimes should be safe for rejection and infectious complications in liver transplant patients.

**Keywords:** Immunosuppression, Liver transplantation

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**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.

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**The Correlation between Pre-operative Volumetry and Real Graft Weight: Comparison of Two Volumetry Programs**

**Keywords:** Hepatic bile salt, Bile acid transporter, Transporter expression, Warm ischemic injury, Non-heart beating donor, Liver transplantation, Tacrolimus, Sirolimus, Rat, Animal study
Liver Transplantation Utilizing a Lacerated Liver

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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 literature 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 segment 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 cirrhosis 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
Recent Advancements in the Pediatric Liver Transplantation: A Single Center Study of 237 Patients Over 27 Years
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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
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 were male and 53.5% were 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 consent (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 transplantation

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.

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 diamefter) 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 in type 1 (0.1%), 0 in type 2 (0.0%), 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.

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**PE - 136**

Salvage Liver Transplantation for Hepatocellular Carcinoma after Laparoscopic or Open Hepatectomy

Seok Hwan Kim1, KI-Hun Kim1, Shin Hwang, Chul-Soo Ahn, Deole Bog Moon, Tae-Yong Ha, Gil-Won Song, Dong-Hwan Jung, Gil-Chun Park, Woo-Hyong Kang, Jae-Hyun Kim1, Eun-Kyung Jwa, Hwi-Dong Joh, Chung-Yong Kyu, Su-Min Ha, Sung-Gyu Lee

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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 23 days 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.
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  
Suk Kyun Hong, Nam-Joon Yi, Hyeyeong Kim, Hyo-Sin Kim, Kyung Chul Yoon, Kwang-Woong Lee, Kyung-Suk Suh  
Department of surgery, Seoul National University College of Medicine, Korea  

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 hepatic artery stenosis (PAS) was developed 8 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 variceal ligation twice for hematemesis and para-centesis 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 (en-to-end anastomosis). The anastomosis of hepatic artery and bile duct was performed routine manner.  

Results: Prooperative 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: Renoporal 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 Suprarehepatic Inferior Vena Cava Stenosis after Deceased Donor Liver Transplantation with Piggy-back Technique  
Tae-Seok Kim, Keun Soo Ahn, Yong Hoon Kim, Hyoung Tae Kim, Koo Jeong Kang  
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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
Long-term Outcomes of Pediatric Living Donor Liver Transplantation Using Pure Laparoscopic Donor Hepatectomy


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 1.4±0.5. Biliary atresia was the most common cause of end-stage liver disease and mean PELD score was 14.5±7.3. 24 patients were performed Laparoscopic Left 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.
Liver, Infectious Disease

**PE - 143**

**Case Series of Hepatitis A Virus Infection Associated with Hemophagocytic Lymphohistiocytosis 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°C. Initial ECG showed sinus tachycardia. Initial laboratory findings were: WBC 18,910/mm³, PLT 297,000/mm³, AST/ALT 836/465 IU/L, T-bil 2.91 mg/dL, CRP 25.30 mg/dL, and procalcitonin 109 ng/mL, RR 20 breaths/min, and BT 36.6°C. 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 analyzed 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. Usually 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
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. (C-E) Expression of significantly enriched gene ontology genes.

**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

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Biochemical Changes in Non-alcoholic Fatty Liver Disease (NAFLD): A Study in Nepalese Population

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1Department of Laboratory Science, Manmohan Memorial Institute of Health Sciences, 2Department of Clinical Biochemistry, Nepal Army Institute of Health Sciences

**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

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**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 diabetes. 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

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**PE - 150**

**Association of Consumption Level of Simple Sugar and Aspartate and Alanine Aminotransferase: A Cross Sectional Observational Study**

Tae Yang Jung, Dae Won Jun1, Joo Hyun Sohn, Jae Yoon Jeong, Chang Hong Lee, Hye Jin Kang, Hye young Lee

Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea.

**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
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\(\text{SAF}\)) allowing the use of an algorithm (fatty liver inhibition of progression \(\text{FLIP}\)) 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 fibrosis (\(p=0.026, 0.000\), 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

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

Myeong Su Chu1, Hyeon Jeong Yun1, Myeong Jun Song1, Seung Won Jung2, Young Seok Kim1, Si Hyun Bae1, Jong Young Choi1, Sang Wook Choi1, Seung Kew Yoon1
Division of Hepatology and Gastroenterology1, Department of Internal Medicine, College of Medicine, Daejeon St. Mary’s Hospital, The Catholic University of Korea, Department of Internal Medicine2, Soon Chun Hyang University Hospital Seoul, Soon Chun Hyang University College of Medicine, Seoul, Korea. Department of Internal Medicine3, Soon Chun Hyang University Hospital Bucheon, Soon Chun Hyang University College of Medicine, Bucheon, Korea, Department of Internal Medicine4, College of Medicine, Seoul St. Mary’s Hospital, The Catholic University of Korea, Department of Internal Medicine5, The Catholic University of Korea, St. Paul’s Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

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\(\text{SAF}\)) allowing the use of an algorithm (fatty liver inhibition of progression \(\text{FLIP}\)) 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).

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Keywords: Nonalcoholic steatohepatitis, SAF, FLIP
had tumor generally localized separately in the left lobe of a liver. 2 (6,7%) patients had metastases crossed to segments of the left lobe of a liver. 28 (93,3%) patients were revealed to have parasitic impairment, 5 (17,8%) of them had parasitic involvement 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 hemipatectomy 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 surgically dependent disease. Radical resection during alveococcosis is able to heal completely majority of patients and brings good results in the further perspective. I wonder alveococcosis liver surgery because I was ill alveococcosis and underwent surgical treatment. Now I’m alive and well.

Keywords: Alveococcosis, Liver, Resection, Chemotherapy

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 surgical treatment.

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/g14912.5 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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**PE - 157**

Surgery for Metachronous Liver Metastases from Stomach Cancer

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Department of Hepatobiliary and Pancreatic Surgery, Yonsei University College of Medicine

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-

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**PE - 156**

Results of Involving of “Roncoleukin” in Autologous Erythrocyte Shells in Patients with Surgical Sepsis (In Vitro Study)

Erlan Sultangareev, Taigalov E.A., Aidarkhan U.T., Mussin N.M.

Chair of Surgery in Internship, Medical University “Astan”, Astana city, Republic of Kazakhstan

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

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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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**Table.** Clinicopathologic characteristics according to treatment modality for liver metastasis

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Surgery (N=33)</th>
<th>Chemotherapy (N=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M : F)</td>
<td>26 : 7 (7.7 : 1)</td>
<td>35 : 5 (7.0 : 1)</td>
<td>0.357</td>
</tr>
<tr>
<td>Age (Stomach cancer, yr)</td>
<td>58.6 ± 9.6</td>
<td>61.2 ± 10.1</td>
<td>0.272</td>
</tr>
<tr>
<td>Age (Liver metastasis, yr)</td>
<td>59.9 ± 9.7</td>
<td>62.6 ± 10.3</td>
<td>0.260</td>
</tr>
<tr>
<td>DFS (m)</td>
<td>14.5 ± 13.6</td>
<td>15.3 ± 18.8</td>
<td>0.855</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>6 (18.2%)</td>
<td>7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>7 (21.2%)</td>
<td>10 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>20 (60.6%)</td>
<td>23 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>Stomach operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>22 (66.7%)</td>
<td>24 (60.0%)</td>
<td>0.630</td>
</tr>
<tr>
<td>Total</td>
<td>33 (100.0%)</td>
<td>40 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Stomach tumor size</td>
<td>4.3 ± 1.6</td>
<td>5.3 ± 2.7</td>
<td>0.060</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (6.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (45.5%)</td>
<td>16 (40.0%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>16 (48.5%)</td>
<td>24 (60.0%)</td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td>0.186</td>
</tr>
<tr>
<td>Differentiated</td>
<td>22 (66.7%)</td>
<td>22 (55.0%)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>8 (24.2%)</td>
<td>17 (42.5%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3 (9.1%)</td>
<td>1 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>LVI (N=62)</td>
<td>18 (60.0%)</td>
<td>25 (78.1%)</td>
<td>0.170</td>
</tr>
<tr>
<td>PWI (N=51)</td>
<td>11 (40.0%)</td>
<td>13 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Recur size</td>
<td>2.5 ± 1.1</td>
<td>2.8 ± 2.4</td>
<td>0.386</td>
</tr>
<tr>
<td>Recur number</td>
<td>&lt;0.999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 (69.7%)</td>
<td>27 (67.5%)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>10 (30.3%)</td>
<td>13 (32.5%)</td>
<td></td>
</tr>
</tbody>
</table>

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 hyperthermia. 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 manage. 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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**PE - 158**

Damage Control Measures In Major Liver Trauma

Muhammad Zakria1, Umar Alvi2

Department of Surgery, Hushain Memorial Hospital, Lahore, Pakistan

**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 mortality. Massive trauma and abdominal

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**PE - 159**

Laparoscopic Bile Duct Exploration with Glissonian Approach and Individual Dissection

Laparoscopic Glissonian Approach : Bile Duct Exploration Using Combination of Glissonian Approach and Individual Dissection

Sam-Youl Yoon, Hyung-Jun Han, Jin-Suk Lee, Tae-Jin Song

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Purpose: Laparoscopic Glossionian approach is very useful method not only in open hepatectomy but also in laparoscopic hepatectomy. Laparoscopic Glossionian 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 Glossionian 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 Glossionian 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. Glossionian 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 Glossionian approach, bile duct exploration with ligation of left hepatic artery and portal vein performed.

Result: This combination method has the advantages of Glossionian 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 Glossionian 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 Glossionian 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. Glossionian 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 Glossionian 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.
The Degree of Liver Fibrosis Assessed Using Transient Elastography Independently Correlates with the Risk of Stroke: A Case-control Study

Young Dae Kim1, DongBeom Song1, Ji Hoe Heo1, Beom Kyung Kim2,3, Jun Yong Park2,3, Do Young Kim2,3, Sang Hoon Ahn2,3, Kwang-Hyub Han2,3, Kwang Joon Kim4,5, Seung Up Kim2,3

1Department of Neurology, 2Department of Internal Medicine, 3Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; 4Severance Executive Healthcare Clinic, 5Severance Check-up Severance Hospital, Yonsei University Health System, Seoul, Korea

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, Fibrotic burden, WTP should be considered for decision-making of curative treatments.

Association Liver Enzymes with Blood Pressure in Diabetic Patients

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1Faculty of Health Sciences, Hokkaido University, Japan; 2Department of Clinical Biochemistry, Nepal Medical College, Nepal; 3Department of Medical Biochemistry, Nobel College, Nepal

Aims: Gamma-glutamyltransferase (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 means SD. p-values less than 0.05 were considered 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) (= 0.07 and 0.128, respectively) and diastolic blood pressure (DBP) (= 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

### Impact of Ledipasvir/Sofosbuvir on the Work Productivity of Chronic Hepatitis C Patients in Asia

**Young-Suk Lim**, Henry Lik Yuen Chan, Yock Young Dan, Mel Hsuan Lee, Eliza Krueger, Seng Tan, Zobair M. Younossi

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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$164M ($358) in Korea, US$17M ($698) 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

### The Role of Endoscopic Ultrasound in a Tertiary Hospital: Past and Present

**Gian Carlo A. Carpio, Ramon E. Carpio, Frederick T. Dy**

Department of Internal Medicine, Section of Gastroenterology, University of Santo Tomas Hospital

**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 (26.2%) 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

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. Polyp-hy-pharmacy 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 contraindicated 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

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
Ja Yoon Heo1, Soo Young Park2, Beom Kyung Kim1,2, Jun Yong Park1,2, Do Young Kim1,2, Sang Hoon Ahn1,2, Won Young Tak3, Young Oh Kweon4, Kwang Hyub Han1,2, Seung Up Kim1,2
1Department of Internal Medicine, 2Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, South Korea; 3Kyungpook National University School of Medicine, Daegu, South Korea

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 analysis in two tertiary medical centers (Severance hospital and Kyungpook National University Hospital). The major end-point was the first EVB event. ARFI-spleen diameter to platelet ratio score (ASPS) was calculated \[\text{ASPS} = \text{ARFI velocity (m/s)} \times \text{spleen diameter (cm)} / \text{platelet count (10^9/L)}\].

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 10^9/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 EVB during follow-up period (median 37 months). To differentiate EVB-risk among patients with HEV, 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 group showed 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 EVB among 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 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
Validation of a Diagnostic Strategy of Combining Liver Stiffness Value by Transient Elastography and Enhanced Liver Fibrosis to Assess Fibrotic Burden in Patients with Chronic Hepatitis B

Ja Yoon Heo1, Beom Kyung Kim1,2, Jun Yong Park1,2, Do Young Kim1,2, Sang Hoon Ahn1,2, Kwang-Hyub Han1,2, Seung Up Kim1,2

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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 ensure a higher chance to avoid liver biopsy (LB). In this study, we assessed the diagnostic performance of LS and ELF, validated LS-ELF diagnostic algorithm, and investigated whether sequential combination of LS and ELF performs better than their concomitant combination in treatment-naive 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 measurement 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 characteristic curve 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, 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 proportion according to the 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 concomitant first-line use in terms of higher chance to avoid LB in patients with CHB.

Keywords: Enhanced liver fibrosis, Liver stiffness

Poster Exhibition

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 third world setting. Thus, the aim of this study is to determine body mass index (BMI) predicts 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 53.2±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.

Average Fibroscore

Body Mass Index Class

www.theliverweek.org 199
Recurrence Patterns of Curative Resected Ampulla of Vater Cancer: Significance of Lymph Node Dissection around Superior Mesentery Artery

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

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.
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.)
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 exosomes (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.
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. They contain cell-specific protein, mRNA, and microRNA. Recent studies showed that exosomal microRNA is stable in blood because exosomes have a protective function against degradation from enzymes, such as RNase. 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. 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). 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. Sugimachi et al. recently 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. Collectively, these data suggest that serum exosomal microRNAs may have a potential for novel serologic biomarkers for HCC.

References
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.
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.)
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.

References

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 neurodegenerative 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 inflammasome.
Inflammasome in Liver Disease

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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. Inflammasome related liver disease

1) Inflammasome activation in alcoholic fatty liver disease (ALD)

In patients with severe alcoholic hepatitis, serum levels of TNF, IL-8 and IL-1β 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-1β, 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 IL1-1β 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-1β expression.\(^1\)
2) Inflammasome activation in Nonalcoholic fatty liver disease (NAFLD)

Inflammasome activation was thought to link with obesity, metabolic syndrome, type II diabetes mellitus and NAFLD. Csak et al.[7] reported upregulation of inflammasome including NLRP3, ASC, pannexin-1 and procaspase-1 mRNA using MCD (methionine-choline deficient) diet model and have shown increased caspase-1 activity and IL-1β 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-1β releases in hepatocyte. PA triggered danger signals from hepatocyte, in turn, activates and releases inflammasome, IL-1β 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) Inflammasome 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-1β 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-β expression and collagen deposition. Gut derived PAMPs or hepatocyte derived DAMPs can activate inflammasome in Kupffer cell and Kupffer cell derived IL-1β contributes to the activation of HSC. In alcoholic liver disease animal model, liver fibrosis was substantially reduced in Casp 1-knock out mice.[14] In NASH, steatosis and fibrosis were substantially reduced in IL-1r-deficinet 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-1β 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 IR induced renal 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. 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.

References

Clinical Science Methodology Workshop 1

Real World Experience from Expert

Chairs: W. Ray Kim (Stanford Univ.)
Jung-Hwan Yoon (Seoul National Univ.)
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.

\[ \text{MELD-Na} = \text{MELD} + 1.32 \times (137-\text{Na}) - [0.033 \times \text{MELD} \times (137-\text{Na})] \]
RCT: From an Idea into a Practice

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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
- Ensureing 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

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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.
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
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

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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 hepatotropic 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.
Clinical Science Methodology Workshop 2

Real World Experience from Expert

How to Prove Cost-effectiveness in My Research

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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.
Symposium 1

Hepatitis C Virus

Chairs: Mark Sulkowski (Johns Hopkins Univ.)
       Young-Hwa Chung (Univ. of Ulsan)
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 reinfecion 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**


Current Strategy for Chronic Hepatitis C Treatment in Korea

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한국의 C형간염 치료전략

정숙향

부산대학교병원 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
농도 측정과 HCV 유전자형 검사 및 유전자형 1형의 경우 유전자형이 1a형 1b형을 확인하는 검사를 시행해야 한다. 우리나라 환자에서 혼한 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.1

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 하루 2회 경구투여)와 NS5A 억제제인 daclatasvir (60 mg 정 하루 1회 경구투여)와 병합요법, sofosbuvir (400 mg 정 하루 1회 투여)와 ledipasvir/sofosbuvir 고용량 복합제(ledipasvir 90 mg/sofosbuvir 400 mg 단일 정제로 하루 1회 투여)이다. HCV 유전자형 1b형 만성 간염 및 대상성 간경변증 환자에서는 daclatasvir + asunaprevir로 2주간 치료하되 치료 전에 NS5A 내성관련변이 검사를 하여 L31, Y93 변이가 없는 경우에 치료를 시작한다.2 이 약제는 간독성이 있을 수 있어 비대상성 간경변증 환자에서는 금기되며 내성관련변이가 치료 전에 존재하거나 HCV RNA 높을 경우 치료방법이 감소함에 유의해야 한다. 그러나 최근 일본에서 보고된 연구결과에 따르면 신기능 장애나 투석 중에 있는 환자에서 안전하게 높은 치료성공률이 보고되고 있어 이들 환자에서 사용가능할 것으로 생각된다. HCV 유전자형 non-1b형에서는 ledipasvir/sofosbuvir로 12-24주간 치료하고 만성간염, 대상성 및 비대상성 간경변증과 간이식 후의 환자들이 적응대상이 된다. HCV 유전자형 2형에서는 sofosbuvir+ribavirin 12주간 치료가 급여적용이 된다. sofosbuvir는 주로 콩팥을 통해 배설되며 사구체 여과율이 30 mL/min 미만이거나 투석을 필요로 하는 말기 콩팥병 환자에서는 금기이다. 또 amiodarone와 병용투여시 심각한 시פק이 발생할 수 있어 금기이다.3

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.4

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 승인되면 좀 더 치료의 선택이 넓어질 것으로 전망한다.

참고문헌

Towards IFN-free Treatment: DCV+ASV for Genotype 1

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유전자 1형 C형간염 치료를 위한 다클라타스비르-순베프라 병합요법

안 상훈
연세대학교 의과대학 내과학교실

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. 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., cure 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 limitations 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 obstacles 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-naïve; 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-naïve 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.\textsuperscript{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%).\textsuperscript{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.\textsuperscript{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.

<table>
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<tr>
<th>Manufacturer</th>
<th>Protease inhibitors</th>
<th>NS5A replication complex inhibitors</th>
<th>Nucleotide NS5B inhibitors</th>
<th>Non-nucleoside NS5B inhibitors</th>
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<td>GS-9857</td>
<td>Ledipasvir*</td>
<td>Sofosbuvir*</td>
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<td>Velpatasvir</td>
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<td>Merck (MSD)</td>
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<td>Elbasvir*</td>
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<td>Samatasvir</td>
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<td>Asunaprevir*</td>
<td>Daclatasvir*</td>
<td>Beclabuvir</td>
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</table>

*: currently on sale

### References

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 preliminary data suggest that some patients who failed to an NS5A 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 sofosbuvir 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/rit) 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 identified 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 DAA combinations (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 plus 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.

www.theliverweek.org 237
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 at baseline.
• The determination of Q80K polymorphism is recommended prior to Simeprevir-based therapy in Genotype 1a 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.

References


Special Lecture 1.

Chair: Yung Sang Lee (Univ. of Ulsan)
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 mainstay of treatment for volume non-responsive episodes of AKI, especially in Europe and Australia. In countries where terlipressin is not available, nor-epinephrine 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.
<table>
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<th>Parameter</th>
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| Baseline SCr       | Stable SCr \( \leq 3 \) months  
If not available, a stable SCr closest to current one  
If no previous SCr at all, use admission SCr |
| Definition of AKI  | \( \uparrow \text{SCr} \geq 26.4 \mu \text{mol/L (0.3mg/dL)} \) in \( \leq 48 \) hours, or  
\( \uparrow 50\% \) from baseline |
| Staging            | Stage 1: \( \uparrow \text{SCr} \geq 26.4 \mu \text{mol/L (0.3mg/dL)} \) or  
\( \uparrow \text{SCr} \geq 1.50-2.0 \times \) from baseline  
Stage 2: \( \uparrow \text{SCr} > 2.0-3.0 \times \) from baseline  
Stage 3: \( \uparrow \text{SCr} > 3.0 \times \) from baseline or  
\( \text{SCr} \geq 352 \mu \text{mol/L (4.0mg/dL)} \) with an acute  
\( \uparrow \geq 26.4 \mu \text{mol/L (0.3mg/dL)} \) 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 \( \downarrow \) in SCr to a value \( \geq 0.3 \text{mg/dL} \) above baseline  
Complete: \( \downarrow \text{SCr} < 0.3 \text{mg/dL} \) from baseline |

**Figure 1.** Revised definition of AKI for cirrhosis

**Management of AKI**

**Diagnosis of AKI**

- Withdrawal of diuretics & nephrotoxic drugs
- Treatment of infection when present
- Blood transfusion for GI bleed
- Volume expansion with albumin
- Close monitoring with daily blood work

**Response**

- Yes → Close follow-up
- No → Treat with vasoconstrictors & albumin if stage ≥ 2 AKI
- Progression

**Figure 2.** Treatment algorithm for AKI in cirrhosis
References

Clinical Hepatology Update: Changes of DDLT Waiting Priority in Korea

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뇌사자 간이식을 위한 간장 응급도 변경
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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 1은 기존의 Status 1에 준하나, 응급도 1의 조건이 임계점 점 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 2는 각 MELD 점수별로 동일혈액형을 우선 배정이며, 응급도 3 이하에서는 응급도내에서 동일혈액형을 우선 배정한다.
7. MELD 점수가 같을 경우에는 재단되는 대기시간은 현 빨드점수 등록시간에 따라서 장기별 점수가 부여된다.
8. 예외적인 MELD점수 부여와 특수한 경우의 등록여부는 간장판과위원에서 결정한다.

변경된 응급도 기준에 따른 뇌사자 간장배분의 형태가 어떻게 개선되는지에 대한 평가가 필요할 것으로 판단되어, 2016년 정책과제로 간장 응급도 기존의 변경 후 간장 배분 양상과 간이식 대기자의 대기시간의 변동사항을 비교함으로서 간장 응급도 기준변경의 효과를 점검하고자 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
전향력 연구6)에 의하면 간경변화에서 1 cm 이하의 결손은 간세포암(14.6%)보다는 재생결절이나 이상성결절, 혈관증이 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 현재의 조영상 주로 고식적인 가돌리늄 조영제를 사용했을 때와 유사한 초기 역동기영상을 제공하고 지연기 영상에서는 간세포사진 조영제의 특성을 보여주기로 국소 간 병변의 검출 및 진단율의 향상을 가져 올 수 있는 장점이 있으며, 많은 연구들은기존의 CT나 고식적인 가돌리늄조영제를 사용한 MRI 보다 우수한 간세포암 검출율을 보여주었다6). 2014년에 개정된 대한간암학회에서는 gadoxetic acid 조영증강 MRI를 간세포암 진단기준에 도입하였으며 작은 국소간결절의 검출에 장점을 지닌 gadoxetic acid 조영증강 MRI의 도입은 1 cm 이하의 간세포암 진단기를 가능하게 한다. 대한간암학회에서는 간단 가이드라인에 의하면 1cm 이하의 간세포암의 경우 두가지 이상 CT와 MRI 검사에서 간세포암의 조영증강기준(동맥기 파열상과 문맥기 지연기에서의 조영제의 채혈)을 만족하고 간염이 잘 조절되고 있음을 지속적인 AFP 상승이 있을 때 진단할 수 있다6). 마찬가지로 최근 JSH (the Japan Society of Hepatology)에서도 간세포시기를 간세포암 진단기준에 도입하였으며, 국외에서의 학회의 간세포암 보고체계인 LI-RADS (Liver Imaging-Reporting and Data System) 2014년 개정판에서도 간세포시기를 간세포암의 보고 진단기준으로 도입하였다8).

하지만 개정된 대한간암학회의 진단 가이드라인에서는 gadoxetic acid의 20% 간세포시기는 단일이 없으며 고식적인 세포외액조영제와 마찬가지로 문맥거나 조영제 주입 후 2분 - 3분의 지연기영상에서의 채혈시간과 진단기준으로 삼고 있으며 이는 대부분의 양안성간소 간질炎은 20분 간세포시기에에서 저속호강도 보임을 감안하여 위양성률을 줄이기 위함이다. 하지만 gadoxetic acid의 경우 조영제 주입 후 1분 정도부터 간세포에 섭취되어 세포외액조영제의 역동기와는 약간 다른 조영증강 양상을 보이며 20분 지연기영상에서 저속호강도로 보이는 간세포암 대부분은 3분 지연기에서 유사하게 보인다. 일부 연구9)에서는 20분 간세포시기를 지연한 3분 영상까지 만을 간세포암 진단기준으로 삼으면 20분 간세포시기를 포함할 때 보이는 모양도는 낮지만 특이도가 상대적으로 높아져 높은 진단정밀도를 유지할 수 있음을 보였으나 최근 보고된 연구10)에서는 2 cm 이하 크기의 만성간질결절 환자에서 발견된 간결점으로 대상으로 gadoxetic acid 조영증강 MRI 상 동맥기 고혈관성과 20분 간세포시기 저속호강도 진단기준이 문맥기나 3분 지연기영상에서의 저속호강도를 사용한 EASL 진단기준보다 높은 민감도를 보여준 반면 유사한 특이도를 보여주어 20분 간세포시기의 중요성이 점차 대두되고 있다.

고식적인 세포외액조영제를 사용한 CT나 MRI 검사에서 1cm 이하의 작은 간세포암은 동맥기에서는 조영증강을 보이나 문맥기나 지연기에서 섭막 현상은 보이지 않는 경우가 많아 간경화에서 매우 혼란하게 보이는 동맥기 단락 (arterio-portal shunt)과의 감별이 어렵다. Gadoxetic acid의 간세포시기뿐만 아니라 문맥기나 3분 지연기에서는 이러한 작은 HCC를 저 신호강도로 보이도록 동맥단 막과의 감별을 용이하게 해주어 1cm 미만의 HCC 진단을 가능하게 해준다6).

Gadoxetic acid의 간세포시기의 또 하나의 장점은 고식적인 CT나 MRI에서는 보이지 않는 동맥기 고혈관성을 가지지 않는 작은 간결점 간세포시기에 보여줄 수 있다는 점이다. 많은 연구를 통해 이들은 이상성결절(dysplatic nodule, DN)이나 조건간세포암임이 발생했으며 이들을 추적관찰하시 동맥기 고혈관성을 가지는 전형적인 간세포암 소견으로 변할 수 있음을 여러 연구들을 통해서 밝혀냈다. 이들 결점의 크기는 0.4 - 4.0 cm으로 보고되었으며 이는 상당수의 1 cm 이하 크기의 지혈관성의 조건간세포암이 포함되어 있음을 의미한다. 이러한 결점은 크기가 10 - 15mm 이상일 때, 지방을 포함할 때, T1 강조영상에서 고신호강도 일때, T2강조영상이나 하산강조영상에서 고신호강도를 보이거나 추적 관찰시 성장속도 빠를 때, 주요 혈관성의 간세포암 소견으로 변할 가능성이 높은 것으로 보고 되었다. 이러한 지혈관성의 간세포시기 저속호강도 결절이 고혈관성 간세포암 소견으로 진행할 수 있는 1년 누적비율 (cumulative rate)은 3.2% - 30.4%로 보고마다 다를 수 있다11,14). 이런 현상은 단단계 분화(multistep hepatocarcinogenesis)을 통한 간암발생으로 해석되며 간세포암 진단에 gadoxetic acid의 도입은 진행성 간암의
전구단계의 조기인자를 가능하게 함을 의미한다. 최근 연구에 의하면 이러한 결절은 간절제술이나 고주파소작술후 다발성 재발암의 원인으로 증명되었다. 하지만 주적 관찰시 이러한 간세포암 저진도결절에서만 전형적인 별관상 간세포암이 발생하는 것은 아니고 특히 소견이 없던 다른 간심질에도 별관상의 간세포암이 생길 수 있으며 간세포암 저진도결절을 가진 간은 이런 결절이 없는 간에 비해 더 흔하게 간세포암 발생이 보고되었다15.

만성간질환환자에서 생긴 간세포결절이 T2강조영상과 확산강조영상에서 고신호강도를 보일때는 간세포암을 시사하는 소견이다. 일부 고등급혈행결절도 고신호강도를 보일수 있으며 병원진단상 조기간세포암과 고등급혈행 성결절과의 갭이 명확하지 않은 경우가 있음을 감안하면 영상만으로 간암발생의 중간단계의 결과의 명확한 갭이 현실적으로 불가능하다. 확산강조영상은 최근 간MRI의 기본 검사로서 널리 사용되고 있으며 높은 간-종양 대조도를 보여주어 소간세포암의 검출에 큰 장점을 보여주고 있다16. 간세포암 진단시 gadoxetic acid와 고식적인 가돌리늄조영제를 사용한 조영증강영상과 확산강조영상의 조합은 간세포암 진단, 특히 1 cm 미만의 작은 간질환의 발견을 용이하게 하고 동맥기상 조영증강이 되지 않는 저혈관성 조기 간세포암이나 동맥기에서만 조영증강되는 작은 간세포암 진단에 도움을 줄 수 있음을 의미한다고17-18.

결론적으로 간 자기공명영상은 병변의 T1, T2강조 정보를 제공하고, 세포외액조영제와 gadoxetic acid와 같은 간 특이조영제를 사용할 수 있고 확산강조영상은 실제로 간질환 진단과 간암 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 미만의 소간세포암의 조기진단이 전 Policies (overall survival)을 향상 시킨다는 근거가 편.gradient 연구는 아직 없다. 저혈관성의 조기 간세포암의 치료는 진행성간암 치료군과 비교시 생존율을 크게 향상시키지 못한다는 연구19이나 진행성간세포암과 조기간세포암의 동시치료는 무게발생존율 (recurrence free survival)은 증가시키나 전체생존율은 증가시키지 못한다는 보고20는 소간세포암이나 조기 간세포암의 치료에 의한적인 시기를 제공할 수 있다. 또한 최근에 나온 일부 연구에서는 고주파치료가 간세포암에 악성도의 증가나 다발성 간세포암의 증가를 유발시킨다는 보고21도 있어 소간세포암의 적극적인 치료에 대해서는 향후 많은 연구가 필요하다22.

References


비알코올지방간(non-alcoholic fatty liver, NAFL)은 단순지방간(simple steatosis)과 간내 지방의 점착과 염증 및 칼세포의 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, 이 중 10-15%는 염증을 동반한 지방간염으로 추정하고 있다. 염증에서 문제가 되는 것은 염증과 섬유화를 동반한 지방간염이며, 지방간염의 일부는 간경변증과 간암으로 진행한다고 알려져 있다.

최근 비알코올지방간 질환(non-alcoholic fatty liver disease, NAFLD)이 사회적으로 야수가 되는 이유는 첫째, 비알코올지방간의 유병율이 급격하게 증가함에 따라 이와 연관된 사회적 비용(검사, 치료)이 급격하게 증가하고 있다는 점이다. 최근 10년간 비알코올지방간 질환이 전파된 약물시장의 규모는 매년 15%씩 증가하고 있다. 둘째, 만성간질환에서 감염성 질환인 B형 및 C형 바이러스 간염에 대한 유병률 감소 및 치료 성적의 향상으로 만성 간질환에서 비알코올지방간 질환이 차지하는 비중이 커졌다. 마지막으로 비알코올지방간 질환은 간질환 뿐 아니라, 섬엽질환 및 당뇨병 발생을 의미 있게 증가시켜 사회적 부담으로 작용한다는 점이다.

비알코올지방간 질환에서 해결되지 않은 문제는 조직검사를 대체할 수 있는 효과적인 진단방법이 아직 확립되지 않았다는 점과 아직 만족할 만한 치료방법이 없다는 점이다. 본 연계에서는 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. 그러나 특이도가 낮다는 단점이 있으며 간내 지방량이 30% 미만인 경우 민감도가 낮다는 단점이 있다. 또한 초음파를 시행하는 검사자에 따라 진단의 편차가 있는 단점이 있다.

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 영상은 Hounsfield unit (HU)라는 단위를 이용하여 얻은 이미지 영상을 표준화 하게 된다. 공기의 경우 -1000 HU, 물의 경우 0 HU, 빨의 경우 1000 HU로 하여 각 조직의 영상의 강도를 표준화 하게 된다. 일반적으로 간의 경우 비장이나 혈관 및 담도 보다 밝게 보이며 60±10 HU를 보이며
되며, 파하지방의 경우 -90 HU를 나타낸다. 간에 지방의 침착이 많아지게 되면 간의 HU가 비장의 HU보다 낮아지는 현상이 발생된다. 일반적으로 간의 HU가 ≤ 40 HU 미만이나 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 간단한다.3 그러나 방사선의 피막이 발생한다는 단점과 CT 기계 회사 및 설치 기관의 센터에 따라 측정값이 달라질 수 있다는 점, 부중 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 전산의 민감도는 63.7-92.2%, 특이도는 81.0-94.9%로 보고되고 있다.4,5 또한 GE, Philips 및 Siemens 등의 주요 MRI 제조 업체들이 상업적인 지방량 측정 프로그램을 개발한 상태로 임상적응이 이전에 비하여 보다 쉬웠다. 그러나 여전히 고가의 장비를 이용하게 되어 임상의료기관에서 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 나눌 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 혈청 cytokeratin-18 (CK18) 분절(refractile)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 신별검사로서의 가능성을 보여주었다. 그러나, 그러나 CK-18의 임상적용의 가장 큰 문제점은 선행연구에서 제시된 기준치(cutoff value)가 연구자마다 매우 큰 차이를 보인다는 점이며, 두 번째로 지방간염을 예측하는 민감도와 특히도가 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 이었으며, 민감도는 약 66%, 특이도는 82%였다. 이러한 이유로 아직 우리나라를 비롯하여 미국간협회에서 비 알코올 지방간의 진단 및 치료를 위하여 일반적으로 CK-18의 점자를 일반적으로 권고하고 있지 않다. 지방간염(NASH)을 예측하는 생화학적 패널 검사들로는 Nahtest, 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 표준자로 구성되어 있다는 장점이 있다. NAFLD fibrosis score는 특정적으로 low cut off value와 high cut off value를 사용하여 low cut off로 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 국가에서 external validation이 되었으며 비교적 다른 섬유화 예측 모델과 비교하여 좋은 예측능력을 보여 주었다. 가족의 동양에서 이루어진 NAFLD fibrosis score를 이용한 external validation 연구의 결과를 보면 high cut off의 양성 예측율이 0.43%로 매우 낮았다. 홍콩에서 162명의 NAFLD 환자를 대상으로 시행한 연구에서, low cut off value에 해당하는 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 off에서 PPV는 43%를 보였다. 일본 코호트의 경우 27.8%가 F3 이상의 진행된 섬유화를 보였다. 한국에서 진진 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 off를 이용한 NPV는 100%로 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 섬유화를 낮은 동양권에서 high cut off를 이용한 PPV의 사용에 대하여는 보다 면밀한 판단이 필요하다.

3. 비알콜요도간질환 진단(조직생검)
현재까지 비알콜요도간질환 진단은 조직검사이다. 그러나 조직검사를 통한 비알콜요도간진단은 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 비알콜요도간연관 간질변증(NASH associated cirrhosis)의 경우 간내 지방이 모두 연소되어 지방이 없을 수 있다(burn out cirrhosis)는 점이다. 이런 경우 원인미상의 간경변(cryptogenic cirrhosis)의 감별이 매우 어렵다. 술의 마시지 없는 환자에서 perisinusoidal fibrosis, ballooning hepatocyte, Mallory-Denk body가 관찰된다면 비알콜요도간연관 간질변증(NASH associated cirrhosis)을 의심할 수 있는 단서가 되겠지만, 이전에 조직생검을 통하여 지방간염(NASH)을 확인된 경우가 아니라면 ‘burned-out cirrhosis’의 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 시행한 간조직생검의 결과의 일치도는 낮으며, 검점을 이용한 조직생검(needle biopsy)과 수술에 의하여 얻어지는 조직생검의 결과는 다르다고 알려져 있다. 수술에 의하여 간조직을 얻는 경우 시행되는 마취 자체에 의하여 미세한 간염이 발생할 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 간단한 정도를 판단하는 간단기준이 제시되고 있으나 아직 통일된 간단기준이 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. 또한 간내 지방의 측정과 염증세포의 침윤 이외에 간세포의 풍선양 변화(ballooning)에 중요한 관심을 두었으며, 특히 zone 3에서의 손상에 중요성을 제시하였다. 그러나 아직 광범위하여 다른 연구자들에 의하여 validation되지 못한된다는 단점이 있다. NAS는 미국의 clinical research network in non-alcoholic steatohepatitis (CRN)에 의하여 제시되었으며, 많은 연구자들에 의하여 임상적 유효성을 확인(validation) 하였다. 그러나 NAS는 지방간염(NASH)을 진단하기 위하여 만들어진 것이 아니며, 지방간염의 약물 임상연구에서 약물의 품질을 평가하기 위하여 만들어진 방법으로 지방간염을 진단하는데 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 경우를 있을 수 있다. 연구에서 명백한 steatohepatitis (NASH) 환자에서 28%는 NAS 점수가 5점 미만이었으며, 명백하게 지방간염이 아닌 환자에서 7%에서 반대로 NAS 점수가 5점 이상이었다. 최근 유럽 fatty liver inhibition of progression (FLIP) 그룹에서 SAF score를 제시하였다. SAF는 Steatosis, Activity (inflammation), Fibrosis를 함께 평가하였으며 NAS 점수체계와 달리 간내 섬유화와 간세포의 풍선양 변화(ballooning)에 가중치를 두어 NASH를 진단할 수 있도록 하였다. SAF 점수는 관찰자간의 차이가 보다 적다는 장점도 가지고 있다. 향후 다양한 진단기준 및 중등도의 평가 방법에 대하여 보다 체계적인 함이가 필요하다고 하였다.

조직생검은 상기의 여러 가지 문제점이 제기되고 있으나 아직 비알코올지방간 질환을 진단하고 치료효과를 판단하는데 현실과 임상에서 gold standard으로 인정받고 있다. 향후 조직학적 진단과 관련되어 가장 큰 이유는 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 위하여는 7-10%의 체중 감량이 필요하다고 보고되고 있다. 그러나 현실에서 지속적인 체중감량을 위한 식이 및 운동 치료가 어려우며, 10%의 체중 감량을 지속적으로 유지하기도 어렵다.

최근 쿠파에서 시행된 저알로로 식이 및 생활습관 교정 연구에서 1년동안 30%의 대상자가 체중감량이 이루어졌다. 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 있으며 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. 그러나 obeticholic acid는 동시에 혈중 콜레스테롤(LDL-cholesterol)의 수치를 의미 있게 상승시켰으며, 혈중 고밀도 콜레스테롤(HDL-cholesterol)의 높도도 감소 시켰다. 최근에 다른 종류의 FXR 강화제(agonist)인 intestinal
specific FXR agonist를 이용한 연구에서 장특이적인 (intestinal specific) FXR agonist는 지방세포 주변의 염증세포 침윤의 감소 및 인슐린 저항성을 개선시켰으며, 간내 지방의 양과 염증을 감소시켰다. 혼미로운 점은 intestinal specific FXR agonist의 경우 콜레스테롤과 콜레스테롤의 농도를 높이지 않았다.21 그러나 향후 사람을 대상으로 하는 연구가 필요한 상태이다.

NOX-1 and NOX-4 inhibitor (GKT137831)의 경우 NOX 1 and 4를 타깃으로 하는 first in class 약물이다. NOX는 염증세포 및 간세포세포에 존재하면서 간내 염증의 생성과 간내 섭유화 발생에 중요한 역할을 하는 물질이다. 동물실험에서 NOX1/4 억제는 간내 염증과 섭유화 염증에 우수한 효과를 보였으며,22 향후 임상시험 결과를 기대하고 있다.

Galectin-3는 glycoprotein 등과 같이 큰 단백질의 갈라트로스 잔여기에 결합하는 탄수화물 결합 단백질의 일종이다. Galectin-3은 면역세포에 경상적인 경우 매우 높은 농도로 발현을 하고 있으나 염증이 발생되는 경우 매우 높은 농도로 증가하게 된다.23 Galectin-3질량체(antagonist)는 현재까지 동물 실험에 우수한 결과를 보여주고 있다. Galectin-3가 없는 결핍 마우스에서 간내 섭유화의 발생이 억제되었다. GR-MD-02 (Galectin Therapeutics, Inc, Norcross, GA, USA)는 아직 정확한 작용 기전이 규명되지 않았으나 galectin에 결합함으로 작용할 것으로 예상되고 있다. 현재 GR-MD-02는 phase II에서 안전성과 효능 평가 임상시험을 진행하고 있으며 결과를 기대하고 있다(ClinicalTrial.gov NCT02462967).

Cenicriviroc (CVC)는 CCR2와 CCR5의 결합체이다. CCR는 chemokine receptor로 단백질, 대식세포 및 간의 콜레스테롤 등의 다양한 면역세포에 발현을 한다. 또한 CCR는 간세포세포의 활성화에도 중요한 역할을 하여 간내 섭유화에도 중요한 역할을 한다고 알려져 있다.23 현재 CVC를 이용한 CENTAUR 임상연구가 바이알코올 지방간 환자를 대상으로 진행중에 있으며,24 CVC의 안전성 및 효과에 대한 결과를 기대하고 있다(ClinicalTrial.gov NCT02217475).

Emricasan (Conatus Pharmaceuticals, Inc., San Diego, CA, USA)은 pancaspase 저해제이다. 이는 apoptosis의 바이알코올 지방간질환에 매우 중요한 방법을 주목하여 바이알코올 지방간질환의 진행에 있어 가장 중요한 간세포의 포스포혈증(hepatocyte ballooning)은 간세포의 사멸의 마커로 인식되어 왔다. 이는 다른 pancaspase inhibitor를 이용한 전염성 및 염증에서 바이알코올 지방간질환에 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. 이는 PPAR-alpha의 경우 간내지방을 감소시고 염증을 완화하는 작용이 있다고 알려져 있다. 그러나 아직 PPAR-delta의 역할에 대하여 알려진 바가 적으나 PPARdelta는 사멸체(mitochondria)의 기능을 향상시키고 지방의 인산화를 촉진하고 인슐린 저항성을 개선시키는 효과가 있다고 알려져 있다. 274명의 지방간 환자를 이용한 대규모 무작위 대조군 연구에서 GFT505의 투여는 간내 염증호전을 이미 있게 감소시키지 못하였다(초록 발표). 그러나 subgroup 분석에서 초기 시작전 NAS 점수가 4점 이상인 경우 GFT505의 투여는 이미 있는 간내 염증 호전을 유도하였다. 현재 GFT505의 임상효과 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 콜레스테롤 합성에 중요한 효소로 콜레스테롤 생성과 약제에 매우 강력한 효과를 보인다. Aramchol은 60명의 조절방법으로 지방간으로 확산된 환자를 대상으로 3개월간 투여한 연구에서 의미 있는 간내 지방량의 감소를 보였다(초록 발표). 그러나 상기의 연구에서 지방간염 환자는 6명(10%)에 불과하였으며 간내 섭유화 감소에 대한 연구결과는 포함되지 않았다. 현재 Aramchol은 240명의 지방간염 환자를 대상으로 phase IIb 임상을 진행하고 있으며 이 연구에서는 간내 염증 뿐 아니라 간내 섭유화 정도를 비침습적으로 판단할 수 있는 지표를 이용하였다(ClinicalTrials.gov NCT02279524).

ASK1은 apoptosis signal regulating kinase 1으로 세포에서 고피치, TGF-β, 및 산화작용 등 다양한 자극에 의하여 활성화 된다. ASK1의 활성화는 38형 및 JNK 경로를 통하여 세포의 사멸과 섭유화를 유도한다고 알려져 있다. 동물 지방간염 모델에서 ASK1 결합체는 간내 지방량의 감소 및 간내 섭유화 감소를 유도하였다. 또한 ASK1 결합체는 치료 감소를 유도하여 인슐린 저항성 개선 및 치료 대사지표의 개선을 유도하였다. 현재 ASK1 antagoniste (GS-4997)은
phase II 임상을 진행 중에 있으며 중동도의 지방간과 진행된 섬유화를 동반한 지방간염 환자를 대상으로 결과를 기대하고 있다(ClinicalTrial.gov NCT02466516).

Lysyk oxidase-like 2 (LOXL2)는 세포의 기질에서 콜라겐의 결합을 강화시키며, 분해를 억제하는 역할을 한다. 간경변 모델에서 LOXL2의 발현은 증가한다. 동물 모델에서 LOXL2 단일 항체는 간내 섬유화를 억제하였다. Simtuzumab (Gilead Sciences, Foster City, USA)은 현재 비알코올지방간 발현에서 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(ClinicalTrial.gov NCT01672866). 또한 동시에 지방간과 연관된 간경변 환자에서 simtuzumab의 안전성과 효과에 대한 Phase IIb 임상 연구를 진행 중에 있다(ClinicalTrial.gov NCT01672879). 상기 연구는 대상성 간경변 환자를 대상으로 최대 6년간 simtuzumab을 투여하여 HVPG의 감소량과 함께 간경변 관련 합병증 발생을 평가하고 있다. 연구는 2024년에 종료될 예정이다.

References

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 페그 인터페론과 리바비린 병합치료가 사용되었다. 하지만, C형간염 바이러스 (HCV)에 직접 작용하는 direct-acting antiviral agents (DAA)가 개발되고 C형간염에 효율적 치료법으로 승인되면 서 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, 가장 잘 해낼 수 있는 약제들을 소개하고자 한다.

본론

현재의 치료

유전자 1형

1. Daclatasvir와 Asunaprevir 병합요법

Daclatasvir (Daklinza®)는 NS5A 억제제로 60 mg 1일을 식사와 관계없이 하루에 한 번 투여하고, asunaprevir (Sunvepra®)는 NS3/4A protease inhibitor (PI)로 100 mg 1일을 식사와 관계없이 하루에 두 번 투여한다. Daclatasvir와 asunaprevir 병합요법의 치료 기간은 24주이다. Daclatasvir와 asunaprevir 병합요법은 유전자 1형 C형간염 중 유전자형 1b형에서만 치료 효과가 입증되어 반드시 치료 시작 전 유전자형과 함께 유전자형을 정확하게 판별할 수
있는 검사가 필요하다. 치료 경험이 없는 유전자1b형 C형 간염 환자 205명을 대상으로 한 daclatasvir와 asunaprevir 24주 병합요법은 90% SVR를 보였다.1 성별, 인종, IL28B 유전자 다형성, 간경변증 유무에 따른 SVR의 차이는 없었다. 이전 치료 경험이 있는 440명의 유전자1b형 환자를 대상으로 한 daclatasvir와 asunaprevir 24주 병합요법에서 이전 치료에 무반응자, 인터페론 부적합/불능성 환자가 각각 82%와 82%의 SVR률을 보였다.1 일반에서 진행된 3상 연구에서는 이전 인터페론/리바비린 치료에 무반응을 보인 87명과 인터페론 부적합/불능성 환자 135명에서 daclatasvir와 asunaprevir 24주 병합요법으로 전체 85%(188/222)의 SVR률을 보였다.2 이전 치료에 무반응이었던 환자군에서는 SVR를 81%(70/87), 인터페론 부적합/불능성 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 동반되어 확인되었으며, 이 변화가 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 반변이 동반된 경우에는 SVR률(39%)이 낮았고, 해당 반변이 없는 경우 SVR율은 94%로 높았다.3 따라서, 치료 전 반드시 NS5A 내성 관련 반변 검사를 시행하고 반변이 검출될 경우에는 daclatasvir와 asunaprevir 병합요법은 권고되지 않는다. Daclatasvir와 asunaprevir 병합 24주 요법의 치료 중 부작용으로 인한 치료 중단은 1%였으며, 5%이상 번발한 부작용에는 두통(15%), 피로(12%), 설사(9%), 구역(8%), ALT 상승(7%) 등이 있었다.3, 4

2. Ledipasvir/sofosbuvir 고정 용량 단일 정제

Ledipasvir/sofosbuvir (Harvoni®)는 NS5A 역제제인 ledipasvir 90 mg와 NS5B 뉴클레오키드 중합효소 역제제인 sofosbuvir 400 mg을 포함하는 고정 용량 단일 정제로 식사와 관계없이 경구로 하루에 한 번 투약한다. 투약 기간은 유전자1형 만성 C형 간염 환자에서 12주나, 과거 치료 경험 있는 대상성 간경변환 환자 및 비대상성 간경변환(치료 경험이 무반응이거나)의 경우 리바비린을 추가하여 12주 투약하거나 ledipasvir/sofosbuvir 단독으로 24주 치료 할 수 있다. 치료 시작 전 림프카 이노스, 연령, IL28B 유전자 다형성 등은 치료 반응에 유의할 영향을 주지 않으며, daclatasvir와 asunaprevir 병합치료의 단일 치료 전 RVR 존재 여부 및 유전자1a형 (1a 혹은 1b)에 따른 SVR률에 차이가 없어 치료 전 별도의 RAV 검사가 필요하지 않고, 유전자1a형에 따른 치료 적용에도 차이가 없다. 치료 경험이 없는 유전자1형 환자 865명을 대상으로 ledipasvir/sofosbuvir 12주 치료를 시행하였을 때 SVR률은 99%었다. 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.3 이전 치료에 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 역제제에 대한 RAV가 14%의 환자에서 발견되었으나, 이들 중 89%에서 치료 반응이 있었다.

국내에 시행된 연구 결과에서는 이전 치료 경험이 없는 93명 환자(초치료 46명, 이전 치료 실패 47명)에서 ledipasvir/sofosbuvir 12주 치료로 99%(92/93)의 SVR률을 보였고, 간경변환 환자에서도 100%의 SVR률을 보였다. 치료 시작 전 22%의 환자에서는 NS5A 역제제에 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%), 불편 (5-6%) 등이 있었다.4

유전자2형
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 복합하여 12주간 매일 치료 투여한다. 국내 환자 129명을 대상으로 한 3상 연구에서 sofosbuvir와 리바비린의 12주 병합요법 SVR률은 97% 이었다.8 국내 연구에서는 sofosbuvir와 리바비린 12주 치료로 간경변환 환자의 SVR률
이 100% 얻으나 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.

항후의 치료

1. Sofosbuvir/velpatasvir

Sofosbuvir/velpatasvir (Epiclusa®)는 sofosbuvir 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 혼란 이상반응으로는 피로, 두통, 구역, 불편증 등이었다.

2. Sofosbuvir/velpatasvir와 GS-9857 병합요법

Sofosbuvir/velpatasvir 단일 정제와 NS3/4A protease inhibitor인 GS-9857 100mg을 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 혼란 이상반응으로는 두통, 피로, 설사, 구역 등이었다.

결론

최근 만성 C형간염의 치료는 빠른 속도로 발전하고 있으며, 항후 정구 항바이러스제의 역할은 점차 확대될 것으로 생각된다. 현재 국내에서 이미 승인된 약제 및 치료법 이외에도 다양한 치료제가 계속 개발되고 있으며, 항후에는 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 엄중되어도 높은 비용으로 인해 국내에서는 사용 허가 및 의료보험 적용이 선별적으로 적용될 수 있다. 임상의사 는 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.

References


Hepatitis B Virus: Changing Antiviral Treatment Strategies: Low Viral Load in Liver Cirrhosis with Hepatitis B Virus

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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., untreated 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.
References

Nonalcoholic Fatty Liver Disease (NAFLD): Non-obese NAFLD Patients

Chairs: Kwon Yoo (Ewha Womans Univ.)
       So-Young Jin (Soonchunhyang Univ.)
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

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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. Although Asians are less obese than Western people, the prevalence of NAFLD and metabolic syndrome is not lower than that of 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.

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. 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. 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. 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.

Recent research has shown that the size of adipocyte and their biological behavior are critical issues in the pathogenesis of metabolic syndrome. 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. Asians have been shown to have larger adipocytes compared to Caucasians and other ethnic groups. 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. 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. Thus, a relatively late trigger to adipocyte expansion may underlie the phenotypic differences between obese and non-obese NAFLD.

Genetic factors as well as environmental factors are important in the development of NAFLD. Recent genome-wide 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. 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. 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.\textsuperscript{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 \( \geq 10 \text{ kg after age 20} \) plays a crucial role in the pathogenesis of NAFLD, especially in non-obese individuals.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3}

In addition to above pathophysiologic interplay, the distinct different compositions of gut microbes are reported between obese and non-obese NAFLD.\textsuperscript{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.\textsuperscript{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).\textsuperscript{24}

**References**


Genetic Aspects of Non-obese NAFLD Patients

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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-containing-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 phosphatidylinositol 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/m². 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

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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.
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.)
Intra-operative Management for Donor Safety during Laparoscopic Donor Hepatectomy

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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 heptectomy 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 heptectomy and surgical mastery in both living donor heptectomy and major laparoscopic heptectomy should be acquired before starting a laparoscopic donor heptectomy program.[1]

Reference

Early Experience of Robotic Donor Hepatectomy: Learn from Pioneer

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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

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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 limb 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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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 치료할 수 있는 장점이 있으며, 간질환의 주요 치료법이다. 뇌사 기증자는 간이식 희망자에 비해 매우 부족하여, 뇌사 기증자의 부족을 보완하는 방법으로 살아있는 사람의 간 일부를 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 대만으로 활성화되어 세계적으로 단기 연구단 가장 많은 생체 간이식을 시행하고 있으며, 국내 생체 간이식 프로그램은 아시아는 물론 세계적으로도 선도적인 역할을 하고 있다. 생체 기증자는 간 기증 후에도 간기능에 이상을 보이지 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. 이로에서는 생체 간기증자의 장기 예후를 살펴보고, 생체간기증자의 안전 및 삶의 질을 향상시킬 수 있는 방안이 무엇인지 살펴보고자 한다.

참고문헌

5. 대한간화학, 간질환 백서
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.5

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. More studies are needed in order to reach an international consensus.

References

Acceptable Guidelines of Liver Transplantation for Advanced Hepatocellular Carcinoma

Chong Woo Chu
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**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

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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

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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, anti-proliferative 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 intra-operative 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

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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.
KASL-KLCA Joint Symposium

Cure of Hepatitis B Virus and Hepatocellular Carcinoma

Chairs: Mong Cho (Pusan National Univ.)
Joong-Won Park (National Cancer Center)
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

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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
Hepatitis Research Center, National Taiwan University, National Taiwan University, Taiwan

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

Ju-Seog Lee
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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://cancer-genome.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.
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

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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 supraregionally 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.
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 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.

Reference

KLCA-KHBPS Joint Symposium

Optimal Management of Recurrent Hepatocellular Carcinoma after Resection

Chairs: Kwan Sik Lee (Yonsei Univ.)
Kyung-Suk Suh (Seoul National Univ.)
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.
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 절환을 모두 고려하여 결정 되어진다. 특히 간세포암종은 어느 암종과 달리 B형 간염, C형 간염, 알코올성 간질환, 특히 간경변증을 동반 하는 것이 대부분이여서 암종 치료 방침을 결정 하는 것이 매우 난해 하며 그로 인해 완치의 여러 가이드라인이 서로 상이한 치료 방법을 제시 하고 있는 것이 사실이다.2-4 그리고 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% 이하이며지만 간절제술과 국소치료술은 근치적 치료로 고려 될에도 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. 간절제술 후 재발 환자에 고려 되고 있는 치료법은 구체적 간이식, 재 간절제술, 국소치료술등이 다시 일차적으로 고려 되어 있고 그에 적합하지 않은 환자에게 고식적 치료가 시행 되고 있다. 하지만 이들에서 어떤 치료가 더 적합한지, 재발 환자에서도 조치의 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 정동맥혈액전술의 근거에 대해 논의해 보고자 한다.

본론
간절제술 후 재발한 간세포암종의 치료가 어떻게 이루어지나는지에 대해 구체적으로 분석한 보고는 거의 없다. 하지만 간절제술 후 재발한 간세포암종에서 이후 수술등의 특정 치료를 한 경우에 대한 분석 연구에서 개발적인 다른 치료를 연급하고 있어 간접적인 경향은 확인 해 볼 수 있다. Zhou 등6의 연구에서 429명의 간절제술 후 추적 되었던 환자 중 276명(64.3%)에서 재발이 확인 되었고 그 중 재 간절제술을 받은 환자는
37명(13.4%)로, 경동맥학화색전선을 받은 환자는 126명(45.6%), 국소치료중을 받은 환자는 45명(16.3%)이었으며, 보존적 치료만 받은 환자는 68명(24.6%)였다. Wu 등2의 연구에서는 1177명의 간절재술 후 추적되었던 환자 중 641명(54.5%)에서 재발이 확인되었고 그 중 재 간절재술을 받은 환자는 149명(23.2%)였으며, 경동맥학
화색전선을 받은 환자는 388명(60.5%), 국소치료율을 받은 환자는 63명(9.8%)이었으며 전신항암치료를 받은 환자
가 10명(1.6%) 보존적 치료만 받은 환자는 6명(0.9%)이었다. Ho 등3의 연구에서는 980명의 간절재술 후 이식 없이 추적 되었던 환자 중 476명(48.6%)에서 간내 재발이 확인 되었고 그 중 재 간절재술을 받은 환자는 54명(11.3%)으며, 경동맥학화색전선을 받은 환자는 254명(53.3%), 국소치료율을 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 조 치료시의 결정과 크게 다르지 않아 재간절재술, 국소치료, 경동맥학화색전선 등의 선택이 치료의 선택과 유사한 분류로 이루어지고 있다는 것을 알 수 있다. 하지만 이들들 서로 비교한 연구가 없어 치료와 같은 전략으로 접근 하는 것이 제한할 간세포암종 환자에서도 적절한지에 대한 논의는 제한된 상황이다. 하지만, Chan 등은 구제적 간이식과 재
간절재술, 재 국소치료를 비교 한 결과를 보고 하였다. 532명의 간절재술 또는 국소치료율 후 추적 되었던
환자 중 288명(54.5%)에서 재발이 확인 되었고 그 중 간내 재발환자들은 183명이었다. 간내 재발 환자 중 구제
간이식을 받은 환자는 19명(10.4%), 재간절재술을 받은 환자는 24명(13.1%)이며 경동맥학화색전선을 받은
환자는 47명(25.7%), 국소치료율을 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 간절재술, 재 국소치료율을 받은
환자의 5년 무재발 생존율은 각각 40%, 19.8%, 10.6%로 재 국소치료율을 받은 환자에 비해 구제적 간이식과 재
간절재술을 받은 환자에서 예후가 유의하게 좋았다. 하지만 이들들에서 MELD 스코어는 의미 있는 차이를 보였기 때문에 이를 보정 하여 확인하였으나 역시 5년 무재발 생존율은 각각 50%, 48%, 11%로 재 국소치료율을 받은 환자에 비해 구제적 간이식과 재 간절재술을 받은 환자에서 예후가 유의하게 좋았다. 다만, 제한된 조건의
후향적 연구로 어느 치료의 우수성을 논하는 것은 적절 하지 않아 이에 대한 더 많은 연구가 필요하다.
간절재술 후 재발한 간세포암종의 국소치료율을 시행한 연구는 고주파열치료율이 주를 이루며, 에탄올주입술과
방등소작술, 고강도감속초음파치료(HIFU) 등이 보고되어 있다. 이들 연구에서 B형 간염이 동반된 경우가
85%(8-96%)로 대부분 동양에서 이루어진 연구임으로 환자의 80%(23-100%)가 Child-Pugh A등급이었고 B가
12%(0-69%)로 간절재술을 받은 환자인 만큼 간기능은 평소로 잘 보존 되어 있었다. 국소치료율 이후 전체
생존 기간과 무병 생존 기간은 각각 48개월(31-66개월)과 10개월(4-17개월)로 보고 되고 5년 생존율은 40%
(28-83%)이었다. 국소치료율 후 완전 치료 반응율은 69-97%까지 보고되었다. 재 국소치료율후 다시 재발한
경우 재 치료 부위 재발이 11%(3-17%), 완전 간내 재발이 66%(37-95%) 그리고 간외 재발이 17%(5-42%)였다.
재 국소치료율 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 보고되었으며 그 중
알파테아백혈을 100 또는 200 ng/mL를 기준으로 하는 것이 대체로 공통적인 생존 관련 인자로 나타났다. 이들
연구는 대부분 후향적 코호트 연구로 재 국소치료율의 의의를 충분히 설명 해 줄 수 없으나 대체로 치료에서
시행 되는 경우와 유사한 정도의 효과와 부작용을 기대 할 수 있다는 정보를 주고 있다. 한 연구에서 재 국소
치료율과 함께 경동맥학화색전선을 시행 하는 것의 의의에 대해 재 국소치료율과 비교한 전향적 조사 연구가
있다.13 139명의 간절재술 또는 국소치료율 후 치료 부위 이외에서 재발한 5cm 이하의 환자를 무작위 배정하여
69명은 국소 치료율과 함께 경동맥학화색전선을 시행하고 70명은 국소치료율을 시행하였다. 1년, 3년, 5년
전체 생존율 재 국소치료율과 함께 경동맥학화색전선을 시행한 경우 94%, 69%, 46%였고 국소치료율만 시행한
경우 82%, 47%, 36%로 의미 있는 차이가 있었다(p = 0.037). 1년, 3년, 5년 무재발 생존율 재 국소치료율과
함께 경동맥학화색전선을 시행한 경우 80%, 45%, 40%였고 국소치료율만 시행한 경우 64%, 18%, 18% 로
의미 있는 차이가 있었다 (p = 0.005). 이는 근치적 치료 후 재발 시 국소치료술과 함께 경도화학계학적한 전단에 의해 시행하는 것이 국소치료술 단독 보다는 유리 할 수 있다는 것을 보여 준다.

조직요에서와 마찬가지로 재발 중앙의 치료에서도 국소치료술은 간절제술과 비교 될 필요가 있다. 이에 대해서는 전향적 조절 연구가 없으며 Chan 등은 간절제술이 우수함, Kawano 등은 국소 치료술이 우수할 수 있음을 보고 하였으나 그 외 많은 연구는 유사하다고 보고 하고 있다.3,4,17,26,27

간 절제술 후 재발한 환자에서 경도화학계학적 전술을 시행 한 경우에 대한 연구는 많지 않다.28-30 Poon 등은 244명의 간절제술 환자 중 105명이 간내 재발을 보였으며 그들 중 재 간절제술을 받은 환자는 11명, 경도화학계학적 전술을 받은 환자는 71명이었고 알고술주입술이 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%였다고 보고하면서 간절제술 환자가 경도화학계학적전술을 받은 환자보다 예후가 좋은 경향을 보였으며(p=0.085) 전신 항암치료나 보존적 치료를 받는 경우 보다 간절제술, 경도화학계학적 전술, 알고술주입술을 받은 환자가 예후가 유의하게 좋다고 보고 하였다. Okazaki 등은 간절제술 후 재발로 경도화학계학적전술을 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 간도반 이외의 혈관을 통해 조영되는 증상이 있었다고 보고 하면서 조영술시에 주의를 요구한다고 언급 하였다. Takayasu 등은 270명의 간절제술을 받은 환자 중 재발하여 경도화학계학적전술을 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 원인 전이 유무였다.

결론
간세포암종은 기저 간질환으로 인해 근치적 치료인 간절제술을 시행 받는 환자에서도 높은 재발률이 보고 되고 있다. 따라서, 이들 재발을 막기 위한 많은 노력을 이루어 왔다. 가장 기본적인 재발의 예방법은 B형, C형 간염을 치료 하는 것이라는 것은 잘 알려져 있다. 하지만 이미 이들 발암 인자에 오랜 기간 노출 된 간세포암 환자에서 재발을 막는데에 원인 질환 치료 만으로는 부족 할 것으로 보이 함야 보내 소라패혈과11 번역 치료,22 비타민 A 유사체 등33,34이 보조 치료로 연구되었다. 하지만 소라패혈은 예방 효과를 증명하지 못했고 비타민 A유사체는 최근에 보다 강력하고 있어 아직 유용성을 확인하기 어렵다. 번역 치료의 경우 최근 국내에서 발표된 연구에서 그 효용성이 입증 되었으나 임상에서 사용 하기에는 여러 제약이 있는 것이 사실이다. 따라서 재발한 환자에 대한 가장 적절한 치료를 통해 예후 향상을 기대 하는 것이 일차적 목표로 하겠다. 안타깝게도 전반적인 바와 같이 재발한 환자에서 어떠한 치료가 가장 적합한지에 대한 연구는 매우 부족하고 따라서 일반적으로 받아들여지는 알고리즘도 없는 상황이다. 하지만 현재까지 보고를 토대로 볼 때 치료 환자에서의 유사한 기준을 통해 치료 방향을 정하여 치료 하는 것은 재발 환자에서도 유용한 방법일 것으로 보이며 향후 이에 대한 많은 연구가 기대된다.

References
Re-resection: Indication and Limitation

Kyung Sik Kim
Dept. of Hepatobiliary Pancreatic Surgery, Severance Hospital, Yonsei University Medical College, Korea

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, 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. 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. 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.

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).
During the period, mean recurrence times was 3.7 ± 1.7 and 94 (47.7%) 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up duration (m)</td>
<td>63.9 ± 31.7</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>171 : 26 (6.6 : 1)</td>
</tr>
<tr>
<td>Age (1st Op.) (yr)</td>
<td>56.1 ± 10.4</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1 ± 3.1</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>HBV</td>
<td>163 (82.7%)</td>
</tr>
<tr>
<td>HCV</td>
<td>16 (8.1%)</td>
</tr>
<tr>
<td>HBV + HCV</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>Non-B, Non-C</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>C-P Classification</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>192 (97.5%)</td>
</tr>
<tr>
<td>B</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>C</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>1st resection</td>
<td></td>
</tr>
<tr>
<td>Major (≥3 segments)</td>
<td>91 (46.2%)</td>
</tr>
<tr>
<td>Minor (&lt;3 segments)</td>
<td>106 (53.8%)</td>
</tr>
<tr>
<td>OS (m)</td>
<td>108.0 (85.5-130.5)</td>
</tr>
<tr>
<td>1st DFS (m)</td>
<td>16.0 (12.0-19.0)</td>
</tr>
<tr>
<td>DmFS (m)</td>
<td>89.5 (82.5-97.2)</td>
</tr>
<tr>
<td>Mean recurrence times</td>
<td>3.7 ± 1.7</td>
</tr>
<tr>
<td>Recurrence treatment portion (n=540)</td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>32 (5.9%)</td>
</tr>
<tr>
<td>LT</td>
<td>14 (2.6%)</td>
</tr>
<tr>
<td>RFA</td>
<td>107 (19.8%)</td>
</tr>
<tr>
<td>TACE</td>
<td>359 (66.5%)</td>
</tr>
<tr>
<td>TARE</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td>RTx.</td>
<td>18 (3.3%)</td>
</tr>
<tr>
<td>Type of treatment modality</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>103 (52.3%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>94 (47.7%)</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of 2nd treatments after recurrence

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (2nd Tx.) (yr)</td>
<td>57.9 ± 10.4</td>
</tr>
<tr>
<td>1st DFS (m)</td>
<td>16.0 (12.0-19.0)</td>
</tr>
<tr>
<td>2nd Tx.</td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>15 (7.6%)</td>
</tr>
<tr>
<td>LT</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>RFA</td>
<td>30 (15.2%)</td>
</tr>
<tr>
<td>TACE</td>
<td>134 (68.0%)</td>
</tr>
<tr>
<td>TARE</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>RTx.</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>TACE + RFA</td>
<td>13 (6.6%)</td>
</tr>
<tr>
<td>2nd DFS (m)</td>
<td>42.0 (35.5-48.5)</td>
</tr>
<tr>
<td>Interval DFS (m)</td>
<td>15.0 (11.4-18.6)</td>
</tr>
</tbody>
</table>

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

References

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 peri-operative 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. 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. 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. 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 chemoembolization (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). 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).

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.
References

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 transplantation 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.
Korea Central Cancer Registry

Chair: Soon Ho Um (President of KLCA)
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

References

Emerging Therapies for Hepatocellular Carcinoma

Chairs: Jae Seok Hwang (Keimyung Univ.)
Jung-Hwan Yoon (Seoul National Univ.)
Searching for Biomarker-driven Therapy for Hepatocellular Carcinoma

Si Hyun Bae¹, Jung-Hee Kwon², Jin Young Park²

¹Division of Hepatology, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea
²Cbs Bioscience Inc, Daejeon, Korea

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

Jeeyun Lee
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 IX 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
Department of Internal Medicine College of Medicine Kyungpook National University, Korea

간세포암에 대한 경피적 절제 치료물의 최신지견
탁원영
경북대학교 의과대학 내과학과

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.
years, respectively.

[2] Nontouch technique

Seror et al. 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°C, which results in freezing the lesion to at least -35°C 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.

[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. 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.

[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. However, a recent meta-analysis 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. 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.

[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. 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. 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.


Some studies have demonstrated that using a contrast agent during RFA improves the accuracy in detecting and targeting HCC. 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%, and additionally the nodules detected by CEUS were positively correlated with the serum albumin concentration.

[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. 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.
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. 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. 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. 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.

References

Emerging Therapies for Hepatocellular Carcinoma


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)
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 Step 1, 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 anatomical 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
간이식은 말기 간절환으로 치료가 불가능한 상태의 환자에게 타인의 간으로 대체하는 수술방법으로 이는 환자의 생명연장뿐 아니라 삶의 질 증진에도 긍정적인 영향을 미치면서 현재에는 가장 확실한 치료 방법으로 그 입지를 굳혀 가지고 있다. 이런 간이식은 정기기증을 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 반도는 빠르게 증가하고 있고, 질병관리본부 정기이식관리센터 통계연보에 따르면 2000년 171건이었던 생체부분 간이식은 2014년 8582건으로 증가하였으며, 2014년 현재 시행된 간이식의 1,262건 중 68.0%를 차지하여 증가가 전망되고 있다. 생체부분 간이식이 활발해 지면서 많은 연구가 이루어지며, 간공여자의 안전 및 신체적 회복, 합병증 예방을 위해 많은 노력을 기울이고 있지만, 아직까지도 많은 연구와 관심은 간이식 수혜자 중심의 삶의 질, 스트레스, 적응능력과 향상에 초점을 두며, 간공여자의 문제는 간고형제 및 신체적 문제와 합병증에 초점을 두고 있다. 공여자를 대상으로 한 연구결과 단순한 간기능회복뿐만이 아닌 신체 기능 회복 및 삶의 질을 평가한 결과 공여자들은 수술 전보다 낮은 신체기능 및 삶의 질을 보였으며, 정보 부족으로 인한 간공여자의 교육 요구도가 정서상의 어려움을 촉발하여òng, 최근 진행된 연구들에게 공여자를 위한 상담 및 교육 프로그램을 활성화해야 한다는 보고들이 나오고 있으나, 실제로 대부분의 간이식을 시행하고 있는 많은 의료기관에서 간공여자를 대상으로 수술과정, 수술 전후 관리, 간공여 후 생활을 위한 문제와 정서적 관리 등에 대한 포괄적인 교육 및 상담 프로그램의 진행이 적극적으로 이루어지지 않고 있는 상태이다. 간공여자들 대상 교육 요구도를 확인한 연구 결과에서도 간공여자들은 간공여 수술 관련, 간공여 후 일상생활 관리, 간공여 후 정서관리, 간공여 후 사회생활 관리 순의 내용에 대한 교육요구를 보였으며, 간공여자의 경험을 확인한 연구결과 심리의 불안정한 환경으로 인한 신체적 기능과 신체의 정서적 어려움을 촉발하는 경향이 정서적 상담의 필요성을 제시하였다. 생체 간이식의 높은 수적도 불구하고 생체 간공여자와의 의사의 협력의 현실은 특정에 제한된 자원과 필요한 제한적 인 정비가 이루어지지 않고 있는 상황이다. 예기치 않은 부작용과 합병증을 겪게 되거나, 수혜자의 경과 악화 혹은 죽음을 지켜볼 수도 있는 공여자들에게 그들의 간병한 경험 및 정신건강과 적응을 위하여 할 수 있는 것이 무엇인지를 고민해 봐야 할 시점에서 관여된 전문인들이 생체 정기기증자의 건강증진을 위하여 교육 및 상담의 활성화에 대한 책임과 의무를 다해야 할 때임을 보장하다.

Reference
응급 간이식의 준비

박 지연
서울성모병원 장기이식센터

급성 간부전(Acute liver failure)이란 기저질환이 없는 사람에서 간소실의 증상발현으로부터 26주 이내에 간기능의 급격한 저하와 함께 혈액응고 및 의식 변화가 나타나는 상태를 의미한다. 또한 만성질환을 가진 환자에서 감염이나 급성 간소실과 같은 상황 인자에 의해 급성 약화 소견을 보이는 환자군을 acute-on-chronic liver failure (ACLF)로 정의한다. 급성 간부전으로 진행되는 경우, 흔히 간기능이 유의하게 떨어지며, 응급 간이식에 대한 준비가 필요하다. 급성 간부전은 사망률이 매우 높아 응급 간이식이 수일 내에 이루어져야만 했는데, 신인원비합병증으로 인한 사망 위험이 매우 높으며, 이식 후 환자의 상태는 이식 후 간질환의 상황을 반영하며, 신생원들도 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 뇌사공여자나 부족한 국내 현실상 생체이식으로 진행하는 경우가 많아 신속하게 기증자의 의학적 검사 결과를 반영하고 청신간감의학과 사회사업팀의 면담을 통하여 기증자로서 적합한 경우에는 국립장기이식관리센터의 응급 생체 간이식에 대한 응급을 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 검사종합 및 적응성 안정지표, 입원기간, 퇴원기간, 간기증후 관리 및 주의사항에 대한 정보를 제공하여 응급으로 진행하는 간이식의 불안감을 최소화할 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
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이식의 역사를 살펴보면 면역학적 거부반응에 대한 치료제의 개발 및 발전 또한 이식의 역사와 함께 이루어졌다고 보아진다. 하지만 오늘날에도 완전하게 이해되지 못하는 이식 거부반응은 계속 존재하고 있으며 이는 장기이식 후 환자 관리에 있어 폐어나가야 할 영원한 과제이다.

Symposium 2

Pros and Cons of LC-Controversial Issues

Chairs: Samuel Lee (Univ. of Calgary)
       Sung Won Cho (Ajou Univ.)
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-responders 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 hemodynamic effect¹. 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 treatment¹. Although the mechanisms underlying the gray zone are not fully understood, the evidences show that both risk and prognosis of variceal hemorrhage 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 important².

Decreased intestinal motility, increased intestinal permeability, and bacterial overgrowth frequently occur in cirrhosis and induce potentially important clinical implications in the domain of BT³. 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 cirrhosis⁴. 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 vasoconstrictors⁵, 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 PHT⁷.

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 pressure⁴. 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’.

**References**

2. La Mura V1, Colombo M. Bacterial translocation and nonselective β-blockers in portal hypertension: where we are, what we still need. Gastroenterology. 2014 Jul;147(1):247-9.
Scoring Systems for Alcoholic Hepatitis

Patrick S. Kamath
Mayo Clinic College of Medicine, USA

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 it 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.
Special Lecture 2.

Chair: Kwan Soo Byun (Korea Univ.)
Hepatitis C Virus: Next Generation of DAAs

Mark Sulkowski
Professor of Medicine
Divisions of Infectious Diseases and Gastroenterology/Hepatology
Johns Hopkins University School of Medicine
Medical Director, Viral Hepatitis Center
Johns Hopkins Hospital
Baltimore Maryland USA

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 pan-genotypic, lacking potent antiviral activity against HCV genotype 3. There are two protease inhibitors in phase 3 clinical trials that are once daily, potent, pan-genotypic drugs: Voxilaprevir (VOX, GS-9857) and ABT-493. Voxilaprevir is being developed as a fixed-dose combination tablet including sofosbuvir and velpatasvir (a pan-genotypic NS5A inhibitor). ABT-493 is being developed as a fixed-dose combination tablet including ABT-530 (a pan-genotypic 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 pan-genotypic 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 pan-genotypic 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.
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 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 26.4 μmol/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.

References

The Current Management of Acute Kidney Injury in Cirrhosis

Soung Won Jeong

Institute for Digestive Research, and Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University Hospital, Seoul, Korea

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>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline sCr</td>
<td>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.</td>
</tr>
<tr>
<td>Definition of AKI</td>
<td>• Increase in sCr ≥3.3 mg/dl (26.5 μmol/L) within 48 hours, or, • A percentage increase in sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days</td>
</tr>
<tr>
<td>Staging of AKI</td>
<td>• Stage 1: increase in sCr ≥3.3 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 5-fold from baseline • Stage 3: increase of sCr ≥8-fold from baseline or sCr ≥8.0 mg/dl (553.6 μmol/L) with an acute increase ≥0.3 mg/dl (26.5 μmol/L) or initiation of renal replacement therapy</td>
</tr>
<tr>
<td>Progression of AKI</td>
<td>Progression to AKI to a higher stage and/or need for RRT Regression of AKI to a lower stage</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>No response Partial response Full response</td>
</tr>
<tr>
<td></td>
<td>No regression of AKI Regression of AKI stage with a reduction of sCr to ≤3.3 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</td>
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</table>

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).

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 fulfillment 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 hypovolemic (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, outpatient 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 follows4,5; 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 definition7 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 NGAL8 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.

References

Role of Heart in Refractory Ascites, Acute Kidney Injury and Hepatorenal Syndrome

Samuel S. Lee
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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.
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.)
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 endovascular 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.

References


Figure 1. 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 reconstruction. 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
Intervention, Dept. of Radiology, Asan Medical Center, Seoul

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.)
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.
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

References

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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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 liver 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 Ultrasound 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 Ultrasound 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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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 cholangiocellular carcinomas, and 12 liver metastases from gastrointestinal 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.
Symposium 3

Nonalcoholic Fatty Liver Disease (NAFLD)

Chairs: Joung-II 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

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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

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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.

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Hepatocellular Carcinoma Development in Nonalcoholic Fatty Liver Disease

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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.
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.
A

A, Craxi 146
A, Streinu-Cercel 146
Abdirakhmanova, Lyazzat 176
Abdugafarov, Said 120
Abdugafarov, Saiitkarim 127, 176, 178
Abergel, Armand 3, 143
AbuTarif, M. 27
Ablyaikhan, Sharmanov 191
Acharya, SK 11, 32
Adeyemi, Adebowale 52
Adilbek, Mukazhanov 120, 178, 191
Afdhal, Nezam H. 147
Agarwal, K 32
Agarwal, Kosh 3, 141, 143
Aghemo, Alessio 142
Ahn, Chul-Soo 50, 59, 122, 168, 183, 184, 367
Ahn, Curi 182, 183
Ahn, Hongkeun 117, 137
Ahn, Hyeong Sik 190
Ahn, Hyo Jun 36, 170
Ahn, Jeonghoon 225
Ahn, Joong Hyun 33
Ahn, Keun Soo 131, 165, 185
Ahn, S.H. 27
Ahn, Sang Bong 29
Ahn, Sang Hoon 11, 20, 24, 29, 32, 36, 37, 46, 57, 71, 81, 96, 99, 140, 147, 159, 165, 168, 173, 196, 198, 199, 233
Ahn, Seon Young 6, 14, 101, 182, 184
Ahn, Sung-Woo 337
Aidos, Kulmaganbetov 174
Ain, Dani 142
Akhetmet, Seidakhmetov 174
Aldosri, Meshal Saleh 49, 65
Aliya, Taganova 174
Alvi, Umar 194
Alzerwi, Nassar 49, 65, 115
Amanzholov, Bakhtiyar 169
Amarsanaa, J. 156
Amrit, Bhandari 132
An, Hee Jung 150
An, Jihyun 19, 34, 36, 152
Ang, Guinevere T. 197
Ariuanaa, S. 144, 156
Arterburn, Sarah 141, 147
Asan, Zheksembayev 120, 178, 191
Ashimkhanova, Aïymkul 85, 150, 176, 178
Asselah, Tarik 3
Assykbayev, Mels 176
Assykanuly, Yermakhan 120, 127, 176, 178, 191
Asykbayev, Mels 120, 127, 178, 191

B

B., Rovgaliyev 178
Baatarkhuu, Oidov 144, 156
Bacaltos, Neil S. 155
Bae, Hyung Gi 88
Bae, S.H. 11, 19, 22, 25, 39, 42, 57, 68, 82, 90, 104, 128, 129, 134, 162, 163, 191
Bae, Si Hyun 327
Baek, Dong Hoon 118
Baek, Min Young 76, 110, 114
Baek, Sangah 138, 148
Baek, Yang-Hyun 26
Bahn, Joonwoo 35, 141
Bai, Daiseq 12
Baigenzhin, A. 180
Baik, Gwang Ho 45
Baik, Soon Koo 42, 60, 67, 81, 82, 101, 153, 173
Balagot, Cynthia A. 155
Balgan, Gantuya 132
Bang, Chang Seok 45
Bang, Ki Bae 101
Bang, Sung Jo 21, 66, 94, 95, 96, 100, 137
Bayarmaa, Nyamaa 131
Baygenzhin, A. 179
Berg, T. 4
Berg, Thomas 35
Bertz, R. 27
Bhatt, Nirmal Prasad 189
Bhatta, Bhup Dev 132
Bhore, R. 25
Bifano, M. 27
Biziya, Nyam 131, 132
Bolormaa, Ch. 144
Borovskiy, Sergey 169
Bourlière, Marc 142
Brainard, Diana M. 3, 28, 141, 142, 143, 147
Brenner, David A. 129
Brown, Robert S. 141
Brunetto, Maurizia 11
Buga, Ion 178
Buggisch, Peter 142
<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buti, Maria</td>
<td>11, 237</td>
</tr>
<tr>
<td>Butt, Zeeshan</td>
<td>171, 172, 175</td>
</tr>
<tr>
<td>Byeon, Hyerim</td>
<td>64</td>
</tr>
<tr>
<td>Byun, Kwan Soo</td>
<td>21, 24, 34, 35, 41, 45, 62, 67, 87, 88, 107, 111, 116, 161</td>
</tr>
<tr>
<td>C, Moreno</td>
<td>146</td>
</tr>
<tr>
<td>Campbell, Andrew</td>
<td>39, 147</td>
</tr>
<tr>
<td>Carpio, Gian Carlo A.</td>
<td>187, 197</td>
</tr>
<tr>
<td>Carpio, Ramon E.</td>
<td>197</td>
</tr>
<tr>
<td>Cathcart, Andrea</td>
<td>11</td>
</tr>
<tr>
<td>Cha, Jung Hoon</td>
<td>104, 129</td>
</tr>
<tr>
<td>Cha, Ra Ri</td>
<td>26</td>
</tr>
<tr>
<td>Cha, Sang-Woo</td>
<td>58, 63, 76, 81, 94, 110</td>
</tr>
<tr>
<td>Cha, Seung Kuy</td>
<td>60, 81</td>
</tr>
<tr>
<td>Chae, Hee Bok</td>
<td>86</td>
</tr>
<tr>
<td>Chae, Yeon Ji</td>
<td>61, 64, 89</td>
</tr>
<tr>
<td>Chan, Henry Lik Yuen</td>
<td>3, 37, 11, 32, 197</td>
</tr>
<tr>
<td>Chang, Ting-Tsung</td>
<td>39, 147</td>
</tr>
<tr>
<td>Chang, U Im</td>
<td>22, 31</td>
</tr>
<tr>
<td>Chang, Yosoo</td>
<td>32</td>
</tr>
<tr>
<td>Chang, Young</td>
<td>5, 20, 44, 109, 115, 117, 107, 137</td>
</tr>
<tr>
<td>Charlton, Michael</td>
<td>147</td>
</tr>
<tr>
<td>Chayama, K.</td>
<td>25, 27</td>
</tr>
<tr>
<td>Chen, Chi-Yi</td>
<td>32</td>
</tr>
<tr>
<td>Chen, Ta-Liang</td>
<td>43</td>
</tr>
<tr>
<td>Chen, Xinyue</td>
<td>39</td>
</tr>
<tr>
<td>Cheon, Gab Jin</td>
<td>12, 47, 56, 67, 70, 96, 113</td>
</tr>
<tr>
<td>Cheong, Jae Youn</td>
<td>11, 74, 106, 109, 110</td>
</tr>
<tr>
<td>Chinburen, J.</td>
<td>156</td>
</tr>
<tr>
<td>Cho, Chan Woo</td>
<td>48, 49, 65, 121</td>
</tr>
<tr>
<td>Cho, Eun Ju</td>
<td>5, 13, 14, 20, 44, 46, 51, 54, 55, 73, 75, 76, 103, 109, 115, 137, 161</td>
</tr>
<tr>
<td>Cho, Eun Young</td>
<td>90, 141</td>
</tr>
<tr>
<td>Cho, Eunae</td>
<td>106, 169</td>
</tr>
<tr>
<td>Cho, Eun-Hee</td>
<td>67</td>
</tr>
<tr>
<td>Cho, Eunjoo</td>
<td>107, 117</td>
</tr>
<tr>
<td>Cho, Hui-Hee</td>
<td>50</td>
</tr>
<tr>
<td>Cho, Hwui-Dong</td>
<td>122, 186</td>
</tr>
<tr>
<td>Cho, Hyeki</td>
<td>5, 14, 20, 13, 44, 46, 51, 109, 115, 117, 137</td>
</tr>
<tr>
<td>Cho, Hyo Jung</td>
<td>74, 106, 109, 110</td>
</tr>
<tr>
<td>Cho, Hyosun</td>
<td>134</td>
</tr>
<tr>
<td>Cho, Hyun Chin</td>
<td>26, 41</td>
</tr>
<tr>
<td>Cho, Jai Young</td>
<td>152</td>
</tr>
<tr>
<td>Cho, Juhee</td>
<td>32</td>
</tr>
<tr>
<td>Cho, Junhyeon</td>
<td>40</td>
</tr>
<tr>
<td>Cho, Ju-Yeon</td>
<td>40, 129</td>
</tr>
<tr>
<td>Cho, Kwang-Hyun</td>
<td>14</td>
</tr>
<tr>
<td>Cho, Kyu Man</td>
<td>169, 187</td>
</tr>
<tr>
<td>Cho, Kyungjoo</td>
<td>167</td>
</tr>
<tr>
<td>Cho, Mee Yon</td>
<td>42, 153</td>
</tr>
<tr>
<td>Cho, Mong</td>
<td>26, 39, 102, 113, 118, 171</td>
</tr>
<tr>
<td>Cho, Soo Jin</td>
<td>32</td>
</tr>
<tr>
<td>Cho, Sung-Bum</td>
<td>106, 162, 187</td>
</tr>
<tr>
<td>Cho, Sung Ki</td>
<td>112</td>
</tr>
<tr>
<td>Cho, Sung-Won</td>
<td>52, 74, 106, 109, 110</td>
</tr>
<tr>
<td>Cho, Won yong</td>
<td>114</td>
</tr>
<tr>
<td>Cho, Wontae</td>
<td>86</td>
</tr>
<tr>
<td>Cho, Yong Kyun</td>
<td>77, 115</td>
</tr>
<tr>
<td>Cho, Young Deok</td>
<td>386</td>
</tr>
<tr>
<td>Cho, Young Youn</td>
<td>58, 63, 76, 81, 94, 110, 114</td>
</tr>
<tr>
<td>Cho, Yuri</td>
<td>5, 13, 20, 44, 46, 51, 54, 55, 76, 109, 111, 115, 117, 137</td>
</tr>
<tr>
<td>Cho, Yoo, Jung Wan</td>
<td>51, 55, 75, 103, 161</td>
</tr>
<tr>
<td>Cho, Won Hyeok</td>
<td>88</td>
</tr>
<tr>
<td>Choi, Byung Hyun</td>
<td>5, 13, 20, 44, 46, 51, 54, 55, 76, 109, 111, 115, 117, 137</td>
</tr>
<tr>
<td>Choi, Byung Jo</td>
<td>167</td>
</tr>
<tr>
<td>Choi, Dae Hee</td>
<td>54</td>
</tr>
<tr>
<td>Choi, Dasom</td>
<td>67</td>
</tr>
<tr>
<td>Choi, Dongho</td>
<td>64</td>
</tr>
<tr>
<td>Choi, Dongil</td>
<td>69, 129</td>
</tr>
<tr>
<td>Choi, Duck Joo</td>
<td>177</td>
</tr>
<tr>
<td>Choi, Eun Young</td>
<td>98, 110, 139, 168</td>
</tr>
<tr>
<td>Choi, Gi Hong</td>
<td>44, 91, 102</td>
</tr>
<tr>
<td>Choi, Gyu-Seong</td>
<td>84, 99, 50, 60, 69, 119, 122, 165, 193, 195, 283, 380</td>
</tr>
<tr>
<td>Choi, Ho Joong</td>
<td>48, 49, 65, 77, 121, 157, 366</td>
</tr>
<tr>
<td>Choi, Hui Chul</td>
<td>162, 186</td>
</tr>
<tr>
<td>Choi, Hwa Young</td>
<td>45</td>
</tr>
<tr>
<td>Choi, Hye Jung</td>
<td>31, 72</td>
</tr>
<tr>
<td>Choi, Hyuk Soo</td>
<td>66</td>
</tr>
<tr>
<td>Choi, Jae Hee</td>
<td>92</td>
</tr>
<tr>
<td>Choi, Jin Sub</td>
<td>133</td>
</tr>
<tr>
<td>Choi, Jin Yong</td>
<td>48, 49, 50, 60, 69, 119, 122, 165, 193</td>
</tr>
<tr>
<td>Choi, Jin-Sub</td>
<td>184, 337</td>
</tr>
<tr>
<td>Choi, Jing-Young</td>
<td>193</td>
</tr>
<tr>
<td>Choi, Jong Ho</td>
<td>182</td>
</tr>
<tr>
<td>Choi, Jong Won</td>
<td>62, 82</td>
</tr>
<tr>
<td>Choi, Jong Young</td>
<td>165</td>
</tr>
<tr>
<td>Choi, JoonHo</td>
<td>19, 22, 36, 57, 68, 90, 104, 128, 129, 134, 163, 191</td>
</tr>
<tr>
<td>Choi, Joon Ho</td>
<td>101</td>
</tr>
<tr>
<td>Author</td>
<td>Page(s)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td></td>
</tr>
<tr>
<td>Daegu-Gyeongbuk Liver Study Group (DGLSG)</td>
<td>71</td>
</tr>
<tr>
<td>Daez, Ma. Lourdes O.</td>
<td>93</td>
</tr>
<tr>
<td>Dahal, Sudimna</td>
<td>189</td>
</tr>
<tr>
<td>Dai, Chia-Yen</td>
<td>149</td>
</tr>
<tr>
<td>Dan, Yock Young</td>
<td>37, 197</td>
</tr>
<tr>
<td>Das, Ranjan</td>
<td>60, 81</td>
</tr>
<tr>
<td>Dashnyam, Baterdene</td>
<td>132</td>
</tr>
<tr>
<td>David Kwon, Choon Hyuck</td>
<td>48, 49, 65, 77, 157, 115, 121, 373</td>
</tr>
<tr>
<td><em>D</em></td>
<td></td>
</tr>
<tr>
<td>Dinh, Phillip</td>
<td>11, 32</td>
</tr>
<tr>
<td>Djajakusuma, Angela D.</td>
<td>155</td>
</tr>
<tr>
<td>Doehle, Brian</td>
<td>147</td>
</tr>
<tr>
<td>Doh, Young Seok</td>
<td>127</td>
</tr>
<tr>
<td>Doskali, M.</td>
<td>179, 180</td>
</tr>
<tr>
<td>Doskaliyev, Zh</td>
<td>179, 180</td>
</tr>
<tr>
<td>Durand, Francois</td>
<td>141</td>
</tr>
<tr>
<td>Duvoux, Christophe</td>
<td>141</td>
</tr>
<tr>
<td>Dvoy-Sobol, Hadas</td>
<td>141, 143, 147</td>
</tr>
<tr>
<td>Dy, Frederick T.</td>
<td>197</td>
</tr>
<tr>
<td><strong>E</strong></td>
<td></td>
</tr>
<tr>
<td>E.A., Taigulov</td>
<td>193</td>
</tr>
<tr>
<td>Eggleton, Edward</td>
<td>142</td>
</tr>
<tr>
<td>Eley, T.</td>
<td>27</td>
</tr>
<tr>
<td>Elkhashab, Magdy</td>
<td>35</td>
</tr>
<tr>
<td>Eom, Young Woo</td>
<td>82</td>
</tr>
<tr>
<td>Erlan, Sultangereev</td>
<td>181</td>
</tr>
<tr>
<td>Eun, Hyuk Soo</td>
<td>61, 75, 130, 139</td>
</tr>
<tr>
<td><strong>F</strong></td>
<td></td>
</tr>
<tr>
<td>F, Tatsch</td>
<td>146</td>
</tr>
<tr>
<td>Fabri, Milotka J.</td>
<td>35</td>
</tr>
<tr>
<td>FANG, Taishi</td>
<td>182</td>
</tr>
<tr>
<td>Feld, Jordan J.</td>
<td>3</td>
</tr>
<tr>
<td>Felix, Jorge</td>
<td>37</td>
</tr>
<tr>
<td>Ferenci, P.</td>
<td>4</td>
</tr>
<tr>
<td>Flaherty, John F</td>
<td>11, 32, 35</td>
</tr>
<tr>
<td>Foster, Graham</td>
<td>143</td>
</tr>
</tbody>
</table>

---

www.theliverweek.org  391
Fredrick, Linda M. 39, 147
Friedman, Richard 52
Fu, Bo 147
Fung, Scott 32, 35

G
Gandhi, Y. 27
Gane, Edward 11, 32
Gane, Edward J. 28, 35
Gang, Cui 182
Gani, Kuttymuratov 176
Gansaikhan, B. 144
Gao, Bing 24, 28
Garimella, T. 27
Garimella, Tushar 39
Gho, Yong Song 203
Gil, Eunmi 77
Gim, Jungsoo 76
Go, Yun-Song 164
Gong, Guozhong 39
Gruener, Norbert 3
Gschwantler, M. 4
Gu, HongDu 131
Gu, Seonhye 32
Guallar, Eliseo 32
Gwak, Geum-Youn 20, 32, 33, 34, 52, 72, 77, 83, 112, 118, 136, 154, 155
Gwak, Mi Sook 77
Gyune, Kim Sang 102

H
Ha, Chang Yoon 26, 41
Ha, Heon Tak 65, 166
Ha, Su-Min 184
Ha, Tae-Yong 50, 59, 122, 168, 183, 184, 367
Ha, Yeonjung 108, 150
Han, Byung Hoon 38
Han, Dai Hoon 49, 60, 69, 122, 193
Han, Dong Wook 69
Han, Hyung-Jun 164, 194
Han, Jae Hyun 68, 133
Han, Ji Won 19, 68
Han, Joong Koo 182
Han, Kwang Hyub 11, 20, 24, 28, 29, 36, 37, 39, 42, 46, 57, 71, 81, 96, 99, 105, 140, 147, 149, 159, 165, 167, 168, 173, 196, 198, 199
Han, Nam Ik 119
Han, Sang-Young 24
Han, Seong-bong 19, 36
Han, Seunghoon 6
Han, Sojung 140
Han, Sung Yong 118
Han, Sung-Sik 64
Han, Xue-Ji 55
Han, Young Seok 65, 166, 284
Hann, Hie-Won 35
He, Shanshan 23
Heo, Ja Yoon 71, 140, 198, 199
Heo, Jeong 24, 26, 34, 39, 113, 171, 118, 147, 320
Heo, Ji Hoe 196
Heo, Jin Seok 77
Heo, Nae-Yun 26, 102, 145
Her, Kyu Hee 177
Herzer, K. 4
Hezode, Christophe 3
Hong, Eun Kyung 53, 64, 136
Hong, Geun 180
Hong, Gun Young 40
Hong, Meeun 45
Hong, Seon-Hui 3, 61
Hong, Seung-Mo 168
Hong, Soon-Chan 121
Hong, Suk Kyun 6, 14, 47, 127, 178, 179, 180, 182, 183, 184, 185, 182, 337
Hong, Sung Yeon 74, 120, 122
Hong, Tae Ho 6
Hong, Young Mi 26, 102, 113, 118, 171
Horban, Andrzej 35
Horsmans, Yves 141
Hsu, Shih-Jer 39
Hu, Jui-Ting 131
Hu, Xu-Guang 74, 120, 122
Hu, Zongyi 23
Huang, Ching-Shan 131
Huang, Chung-Feng 149
Huang, Jee-Fu 149
Huang, May-Jen 131
Huh, Kyu Chan 174, 175
Hui, Aric Josun 11, 32
Hur, Wonhee 83, 104
Hwang, Chae Young 14
Hwang, Ho Kyoung 67
Hwang, Hong Pil 66
Hwang, Jae Chul 74
AUTHOR INDEX

Hwang, Jae Seok 32, 34, 71
Hwang, KeumBit 83
Hwang, Kyung Hee 60, 81
Hwang, Moon Joo 71
Hwang, Sang Youn 26
Hwang, Seawon 163
Hwang, Seo Yeon 172
Hwang, Seong Gyu 42, 62, 108, 149, 150, 169
Hwang, Seong Kyu 159
Hwang, Shin 50, 59, 122, 168, 183, 184, 309, 367
Hwang, SunJin 142, 143
Hwang, Yoon Jin 65, 166
Hwang, Yu Ri 88
Hyeon, Dong Lee 91
Hyland, Robert H. 142, 143
Hyun, Jong Jin 88, 107
Hyun, Ju Shin 152
Hyung, Tae Kim 87, 95

I

Ibrayev, Baurzhan 150
Il, Joo Jung 65
Im, Jong Hun 51, 55
Im, Sanghyuk 22, 40, 58, 72, 84, 152
Ingliz, P. 4
Ingliz, Patrick 142
Ismael, Albert E. 197
Izumi, Namiki 11

J

Jacobson, Ira M. 3
Jadoon, Nauman Arif 171, 172, 175
Jae, Yang Min 74
Jamias, Jade D. 155
Jang, Bo Hyun 22, 57, 68, 163
Jang, Byung Kuk 11, 34, 71
Jang, Eun Sun 22, 38, 40, 58, 84, 152
Jang, J.Y. 25
Jang, Jae Yool 121
Jang, Jae Young 12, 42, 42, 44, 47, 56, 58, 63, 70, 76, 81, 94, 96, 102, 105, 110, 113, 114
Jang, Ja-June 14
Jang, Jeong Won 5, 19, 22, 36, 57, 68, 104, 115, 119, 163, 219
Jang, Jin-Young 64, 200

Jang, Ki Seok 61, 64, 89
Jang, Min Uk 45
Jang, Myoung Kuk 87, 91, 164, 143, 192
Jang, Se-Jin 151
Jang, Suk Hyun 174, 175
Jang, Sungho 69, 129
Jang, Yoon Ok 42, 101
Janssen, Harry 11
Janssen, Harry L.A. 32
Je, Ji Hyo 41, 62, 111, 116, 161
Jekarli, Dong Wook 57
Jeon, Dae Young 65
Jeon, Hyeryeon 69, 129
Jeon, Jang Yong 65, 181
Jeon, Mi Young 140, 173
Jeon, Tae Joo 88
Jeon, Ung Baе 171
Jeon, Yong Chul 91
Jeon, Youn Ju 92
Jeong, Chi-Young 121
Jeong, In Du 21, 94, 95, 96, 100, 137
Jeong, Jae Yoon 12, 29, 61, 64, 89, 189, 190
Jeong, Jaehong 157, 178, 179, 180, 183
Jeong, Jaemin 69, 129
Jeong, Seoung Won 63, 81
Jeong, Sook-Hyang 22, 24, 38, 39, 40, 58, 72, 84, 146, 152, 231
Jeong, Soung Won 11, 12, 44, 47, 56, 58, 70, 76, 94, 96, 102, 105, 110, 113, 114, 356
Jeong, Sung Hoon 187
Jeong, Won-il 61
Jeong, Wonjun 54
Jeong, Woo Kyoung 177
Jeong, Yong-Yeon 90
J-F, Dufour 146
Jia, Jidong 39
Jia, Zhanheng 39
Jian, Hong 103
Jimenez-Exposito, M.J. 4
Jin, Hyun Kim 26
Jin, Xueli 183
Jin, Young-Joo 156
Jo, Jin Beom 186
Jo, Sang-Kyu 86
Jo, Se Hyun 22
Jo, Soo Yeon 159
Joh, Hwi-Dong 184
Joh, Jae Won 48, 49, 77, 115, 131, 121, 157
Joh, Jae-Won 65
<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joo, Dong Jin</td>
<td>48, 49, 50, 119, 122, 294</td>
</tr>
<tr>
<td>Joo, Jong Seok</td>
<td>61, 75, 130, 139</td>
</tr>
<tr>
<td>Joo, Jungnam</td>
<td>117</td>
</tr>
<tr>
<td>Joo, Min Soo</td>
<td>90, 141</td>
</tr>
<tr>
<td>Joo, Min Sun</td>
<td>86</td>
</tr>
<tr>
<td>Joo, Sae Kyung</td>
<td>29, 30, 31, 63, 89, 91, 188</td>
</tr>
<tr>
<td>Joo, Young-Eun</td>
<td>114</td>
</tr>
<tr>
<td>Jorge, Jenina Joy E.</td>
<td>187</td>
</tr>
<tr>
<td>Ju, Man Ki</td>
<td>48, 50, 119</td>
</tr>
<tr>
<td>Ju, Se Kyung</td>
<td>190</td>
</tr>
<tr>
<td>Ju, Yeonmi</td>
<td>87</td>
</tr>
<tr>
<td>Jun, Baek Gyu</td>
<td>96, 113</td>
</tr>
<tr>
<td>Jun, Chung Hwan</td>
<td>40, 90, 106, 114, 169, 187</td>
</tr>
<tr>
<td>Jun, Dae Won</td>
<td>12, 29, 61, 89, 92, 189, 190, 256</td>
</tr>
<tr>
<td>Jun, Hong Young</td>
<td>90</td>
</tr>
<tr>
<td>Jun, Jongsoo</td>
<td>161</td>
</tr>
<tr>
<td>Jun, Mi-Jung</td>
<td>152</td>
</tr>
<tr>
<td>Jung, Dong Hae</td>
<td>110</td>
</tr>
<tr>
<td>Jung, Dong-Hwan</td>
<td>50, 59, 122, 183, 184, 367</td>
</tr>
<tr>
<td>Jung, Eun Sun</td>
<td>42</td>
</tr>
<tr>
<td>Jung, Hyun Suk</td>
<td>112, 115</td>
</tr>
<tr>
<td>Jung, Kyu Sik</td>
<td>96, 159</td>
</tr>
<tr>
<td>Jung, Nuri Hyun</td>
<td>161</td>
</tr>
<tr>
<td>Jung, Seok Won</td>
<td>21, 94, 95, 96, 100, 128, 137</td>
</tr>
<tr>
<td>Jung, Seung Won</td>
<td>191</td>
</tr>
<tr>
<td>Jung, Su Hee</td>
<td>104</td>
</tr>
<tr>
<td>Jung, Sung Won</td>
<td>133</td>
</tr>
<tr>
<td>Jung, Sung Woo</td>
<td>88, 107</td>
</tr>
<tr>
<td>Jung, Tae Yang</td>
<td>189</td>
</tr>
<tr>
<td>Jung, Woo Jin</td>
<td>58, 94</td>
</tr>
<tr>
<td>Jung, Woon Tae</td>
<td>26, 41</td>
</tr>
<tr>
<td>Jung, Yong Jin</td>
<td>31, 89, 190</td>
</tr>
<tr>
<td>Jung, Young Kul</td>
<td>21, 35, 41, 42, 44, 45, 62, 67, 87, 88, 102, 107, 111, 116, 139, 161, 162</td>
</tr>
<tr>
<td>Jung, Yusun</td>
<td>151</td>
</tr>
<tr>
<td>Jwa, Eun-Kyong</td>
<td>50, 184, 186</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, Dae Yong</td>
<td>74, 106</td>
</tr>
<tr>
<td>Kang, Danbee</td>
<td>32</td>
</tr>
<tr>
<td>Kang, Hye Jin</td>
<td>189</td>
</tr>
<tr>
<td>Kang, Hyeon Tae</td>
<td>61, 64, 89</td>
</tr>
<tr>
<td>Kang, Hyunje</td>
<td>13</td>
</tr>
<tr>
<td>Kang, Jeong Hee</td>
<td>340</td>
</tr>
<tr>
<td>Kang, Koo Jeong</td>
<td>131, 165, 185</td>
</tr>
<tr>
<td>Kang, Kyojin</td>
<td>69, 129</td>
</tr>
<tr>
<td>Kang, Seong Hee</td>
<td>20, 44, 46, 109, 115, 137</td>
</tr>
<tr>
<td>Kang, So Hee</td>
<td>129, 172</td>
</tr>
<tr>
<td>Kang, Sun Hyung</td>
<td>75</td>
</tr>
<tr>
<td>Kang, Wonseok</td>
<td>20, 33, 72, 83, 112, 118, 136, 154, 155</td>
</tr>
<tr>
<td>Kang, Woo-Hyeong</td>
<td>59</td>
</tr>
<tr>
<td>Kang, Woo-Hyoung</td>
<td>50, 183, 184</td>
</tr>
<tr>
<td>Kang, Woo-Hyoung</td>
<td>186</td>
</tr>
<tr>
<td>Kang, Yang Jun</td>
<td>114</td>
</tr>
<tr>
<td>Kang, Young Woo</td>
<td>174, 175</td>
</tr>
<tr>
<td>Kao, Jia-Horng</td>
<td>24, 28, 39, 147, 299</td>
</tr>
<tr>
<td>Karino, Y.</td>
<td>27</td>
</tr>
<tr>
<td>Kaster, Baizhanuly</td>
<td>178</td>
</tr>
<tr>
<td>Kato, Yutaru</td>
<td>377</td>
</tr>
<tr>
<td>Kawaguchi, Yoshikuni</td>
<td>379</td>
</tr>
<tr>
<td>Kawakami, Y.</td>
<td>27</td>
</tr>
<tr>
<td>Khan, Saif U</td>
<td>175</td>
</tr>
<tr>
<td>Khanal, Puspa</td>
<td>188</td>
</tr>
<tr>
<td>Ki, Moran</td>
<td>31, 72, 146</td>
</tr>
<tr>
<td>Kim, Beom Hee</td>
<td>22, 40, 58, 72, 84, 152</td>
</tr>
<tr>
<td>Kim, Beom Kyung</td>
<td>20, 29, 36, 37, 44, 57, 71, 96, 99, 81, 140, 159, 168, 173, 196, 198, 199</td>
</tr>
<tr>
<td>Kim, Bo Hyun</td>
<td>31, 53, 74, 106, 108, 117, 136, 158, 159</td>
</tr>
<tr>
<td>Kim, Bong Wan</td>
<td>74, 110, 120, 122</td>
</tr>
<tr>
<td>Kim, Boo Sung</td>
<td>12, 47, 56, 58, 63, 70, 76, 81, 94, 96, 110, 105, 113, 114</td>
</tr>
<tr>
<td>Kim, Byeong Gwan</td>
<td>29, 31, 89, 91, 190</td>
</tr>
<tr>
<td>Kim, Byung Gyu</td>
<td>21, 94, 95, 96, 100, 137</td>
</tr>
<tr>
<td>Kim, Byung Ik</td>
<td>11, 42</td>
</tr>
<tr>
<td>Kim, Byung Seok</td>
<td>34, 42, 71, 138, 148</td>
</tr>
<tr>
<td>Kim, Byung-Ho</td>
<td>52, 153, 154, 160</td>
</tr>
<tr>
<td>Kim, Chang Jae</td>
<td>100, 13, 21, 94, 95, 96, 128, 137</td>
</tr>
<tr>
<td>Kim, Chang Wook</td>
<td>22, 35, 42, 44, 102, 128, 134, 134, 160, 172</td>
</tr>
<tr>
<td>Kim, Chang-Min</td>
<td>108, 117, 136, 159</td>
</tr>
<tr>
<td>Kim, Chulho</td>
<td>45</td>
</tr>
<tr>
<td>Kim, Chung Yong</td>
<td>13, 14, 76, 103, 109</td>
</tr>
<tr>
<td>Kim, Dae Ghon</td>
<td>54, 55, 93, 170</td>
</tr>
<tr>
<td>Kim, Daeyoung</td>
<td>149</td>
</tr>
</tbody>
</table>
Kim, Do Young 20, 29, 36, 37, 46, 57, 71, 81, 96, 99, 140, 159, 162, 165, 168, 196, 198, 199
Kim, Dong Goo 6
Kim, Dong Hyun 65
Kim, Dong Joon 11, 44, 45, 67, 87, 91, 102, 143, 164, 192
Kim, Dong Uk 118
Kim, Donghee 26
Kim, Dong-Sik 68, 133
Kim, Doo Hyun 133
Kim, Doo Jin 181
Kim, Eun Jeong 138, 148
Kim, Eun Nam 62
Kim, Eung Kook 165
Kim, Ga Young 138, 148
Kim, Gi Dae 82
Kim, Gi Jin 62, 82
Kim, Gi-Ae 19
Kim, Gundo 131
Kim, Haak Cheoul 90, 141
Kim, Haeryoung 152
Kim, Han Gyeol 109
Kim, Hee Yeon 22, 44, 102, 128, 134, 160, 172
Kim, Hong Bin 40
Kim, Hong Ja 101
Kim, Hong Jun 26, 41
Kim, Hong Soo 12, 42, 42, 47, 56, 58, 63, 70, 76, 81, 94, 96, 105, 110, 113, 114, 200
Kim, Hongbeom 200
Kim, Ho-Shik 129
Kim, Hwi Young 44, 73, 102
Kim, Hye Ji 22, 112, 119
Kim, Hye Soo 140
Kim, Hyemi 81
Kim, Hyeyoung 6, 14, 47, 127, 157, 178, 179, 180, 181, 182, 183, 184, 185, 337
Kim, Hyo-Cheol 109, 182
Kim, Hyon-Suk 71
Kim, Hyo-Sin 6, 14, 47, 127, 178, 179, 180, 181, 182, 183, 184, 185, 337
Kim, Hyoung Su 87, 164, 143, 192
Kim, Hyoung Tae 185
Kim, Hyun Jin 41
Kim, Hyun Jung 190
Kim, Hyun Uk 104
Kim, Hyung Don 19
Kim, Hyung Joon 11, 32
Kim, Hyunkyoung 32
Kim, Hyunsoo 76, 161
Kim, In Hee 35, 38, 93, 170
Kim, In-Gyu 120, 122
Kim, Ingyu 74
Kim, Jae Kyung 42, 85, 99
Kim, Jae Keun 74, 165
Kim, Jae Ri 200
Kim, Jaehyung 68
Kim, Ja Keun 106
Kim, Ja-Kyung 11
Kim, Jeong Han 98, 135, 136
Kim, Jeong Min 34
Kim, Ji Chang 170
Kim, Ji Hee 31, 81
Kim, Ji Hoon 21, 35, 39, 41, 45, 62, 67, 87, 88, 107, 111, 116, 161, 310, 74
Kim, Ji Hyun 190
Kim, Ji Won 145
Kim, Ji Yeoun 128, 134
Kim, Ji Young 117
Kim, Jieun E 60
Kim, Ji-Hee 109
Kim, Ji-Hyun 109
Kim, Jin Jo 26, 41
Kim, Jin Sook 53
Kim, Jin Woo 109
Kim, Jin Woong 114
Kim, Jin Yong 136
Kim, Jin-Sun 151
Kim, Jin-wook 22, 40, 58, 72, 84, 133, 152
Kim, Jong Hoon 161
Kim, Jong In 51, 55
Kim, Jong Man 48, 49, 65, 77, 121, 157, 292
Kim, Jonghwa 129, 172
Kim, Jong-Hyun 22
Kim, Joo Seop 181
Kim, Joo Young 68, 133
Kim, Ju Hyun 98, 110, 139, 168
Kim, Ju Seok 130
Kim, Ju-Hyun 24
Kim, Jung Hee 20, 33, 72, 112, 118, 136, 154, 155
Kim, Jung Ho 4, 91
Kim, Jung Oh 149
Kim, Jung-Hee 83
Kim, Kang Mo 36, 127, 151, 152
Kim, Kee-Hwan 54
Kim, Ki Yeon 155
Kwon, Young Woon 112, 115, 119  
Kim, Young-Kyu 64, 177  
Kim, Youngsoo 76, 161  
Kim, Yun Hui 128, 134  
Kim, Yun Soo 98, 110, 139, 168  
Kim, Yun-A 54  
Kim, Yung Jung 40  
Kitrinos, Kathryn M. 32, 35  
Klinker, H. 4  
Knox, Steven J. 143  
Ko, Eunjung 62  
Ko, Frankie Chi Fat 53  
Ko, Gi-Young 368  
Ko, Soon Young 136  
Koh, Kwang Cheol 20, 33, 72, 83, 112, 118, 136, 154, 155  
Kojima, Masayuki 377  
Kokudo, Norihiro 371, 379  
Koo, Bo Kyung 91  
Koo, Hoon Sup 174, 175  
Koo, Ja Seol 88, 107  
Kowdlely, Kris 142  
Kreter, Bruce 142  
Krishnan, Preethi 84  
Kruger, Eliza 197, 198  
Kulmaganbetov, A. 180  
Kumada, H. 25, 27  
Kumar, Princy 141  
Kuttymuratov, Gani 120, 127, 169, 176, 178, 191  
Kweon, Young Oh 34, 71, 198  
Kwo, Paul 141  
Kwon, Hyung Moo 13  
Kwon, Hyung Jun 65, 166  
Kwon, Jae-Hyun 50, 184, 186  
Kwon, Jung Hee 92  
Kwon, Jung Hyun 11, 112, 115, 119  
Kwon, Jung-Hee 110, 131, 327  
Kwon, Oh Sang 98, 110, 139, 168  
Kwon, Song Ok 101, 173  
Kwon, So Young 11, 34, 35, 98, 135, 136  
Kwon, Su-kyung 48, 49, 119, 122  
Kwon, Wooli 200  
Kyu, Chung-Yong 184  
Kyung, Koo Bo 30  

Lai, Ching-Lung 3  
Lawitz, Eric J. 143  
Lazo, Mariana 32  
Lee, Ah Ram 133  
Lee, Bo Kyung 159  
Lee, Bora 12, 47, 56, 70  
Lee, Byung Seok 42, 61, 75, 86, 130, 139  
Lee, Byung Uk 21, 94, 95, 96, 100, 137  
Lee, Byung Wook 66  
Lee, ByungSeok 38  
Lee, Chang Hong 12, 29, 61, 64, 89, 189, 190  
Lee, Chang Hun 93, 170  
Lee, Chang Hyeong 34, 71, 138, 148  
Lee, Chang Min 26, 41  
Lee, Chang-Hyeong 42  
Lee, Chung Seok 22, 40, 58, 72, 84, 152  
Lee, Danbi 19, 36, 152  
Lee, Dong Hyeon 13, 31, 33, 51, 55, 63, 73, 76, 89, 117, 161, 188, 190  
Lee, Dongwon 107  
Lee, Eamr Seok 61, 75, 130  
Lee, Eui-Kyung 195  
Lee, Eun Byul 83, 104  
Lee, Ga Ram 109  
Lee, Hae Lim 19, 22, 112, 119, 145, 14, 47, 178, 180, 182, 183, 289  
Lee, Hae Won 21, 45, 67, 77, 87, 88, 95, 133, 19, 34, 36, 151, 152  
Lee, Han Ah 58  
Lee, Hee Jeong 34, 71  
Lee, Heon Ju 54  
Lee, Hua 13  
Lee, Hwan Hee 20, 29, 37, 99, 140, 147, 168, 173  
Lee, Hyeon Chul 138, 148  
Lee, Hyesun 138, 148  
Lee, Hyo young 189, 190  
Lee, Hyun Gyu 81  
Lee, Hyun Jae 101  
Lee, Hyun Seung 22  
Lee, Hyung Soon 165  
Lee, Hyun-Jung 62  
Lee, Jae Geun 48, 49, 50, 119, 122  
Lee, Jae Hyun 101  
Lee, Jae Min 26, 41  
Lee, Jae Yik 58  
Lee, Jaemin 94  
Lee, Jai Sun 61, 64, 89  
Lee, Jee Youn 48, 49, 119, 122  

L, Liu 146  
LaCreta, F. 27
Lee, Jeewon 61
Lee, Jeeyun 328
Lee, Jei Hee 74, 106
Lee, Jeong Min 111
Lee, Jeong Rok 136
Lee, Jeong-Hoon 13, 14, 20, 33, 44, 46, 5, 51, 54, 55, 73, 75, 76, 103, 107, 109, 111, 115, 117, 137, 161
Lee, Ji Hyeon 33, 118
Lee, Ji Soo 49, 65
Lee, Jin-Suk 194
Lee, Jin-Woo 39, 11, 156, 276
Lee, Jisoo 48, 121
Lee, Jisun 177
Lee, Jong Ho 88
Lee, Jong Joon 168
Lee, Jonghwan 49, 65
Lee, Jong-Yul 112, 115
Lee, Joo Ho 108, 138, 150, 152, 169
Lee, Joon Ho 83
Lee, Joon Hyeok 20, 33, 72, 83, 112, 118, 136, 154, 155
Lee, Ju Ho 149
Lee, Ju Hyun 22, 40, 58, 72, 84, 152
Lee, Juhan 48, 49, 50, 119, 122
Lee, Jun Ho 13, 104
Lee, Jun Suh 112, 119
Lee, June Sung 146
Lee, Jung Hoon 98
Lee, Jung Hwan 51, 55
Lee, Jung Il 85, 99, 148
Lee, Jung Jun 48, 50, 119
Lee, Jung Woo 65
Lee, Jung-Dong 74, 106
Lee, Ju-Seog 52, 300
Lee, Juyoung 22
Lee, Kee Myung 74, 106
Lee, Kook Lae 31, 89, 190
Lee, Kwan Sik 11, 24, 85, 99
Lee, Kwang Jae 106
Lee, Kwang-Woon 47
Lee, Kwang-Woong 6, 14, 48, 75, 78, 111, 115, 127, 157, 179, 180, 181, 182, 183, 184, 185, 337
Lee, Kyung Bun 14
Lee, Kyung Hoon 92
Lee, Kyung Jin 159
Lee, Mei Hsuan 37, 197
Lee, Mi-Jin 54, 55
Lee, Min Jong 54, 67, 111, 117
Lee, Moon Won 113
Lee, Myeong Su 90
Lee, Myoung Seok 4
Lee, Myung Eun 337
Lee, Myung Seok 35, 86, 87, 143, 164, 192
Lee, Nuri 48, 65, 121
Lee, Ok Jae 26, 41
Lee, Sae Hwan 12, 42, 47, 56, 58, 63, 70, 76, 81, 86, 94, 96, 103, 105, 110, 113, 116
Lee, Samuel S. 347, 360
Lee, Sang Chul 54
Lee, Sang Kuon 54
Lee, Sang Soo 26, 41
Lee, Sang Uk 38
Lee, Sang Woo 88, 107
Lee, Sang Yup 104
Lee, Sang-wook 161
Lee, Seung Bum 26, 171
Lee, Seung Duk 64
Lee, Seung Hwa 88
Lee, Seung Hwan 77, 115
Lee, Seung Min 149
Lee, Seung Ok 93, 170
Lee, Soo Teik 93, 170
Lee, Sook-Kyung 53
Lee, Su Gyeong 128, 134
Lee, Su hyun 71
Lee, Su Lim 160
Lee, Sukyoung 160, 172
Lee, Sung Won 19, 112, 119
Lee, Sung-Gyu 50, 59, 122, 152, 168, 183, 184, 367
Lee, Sungyoung 161
Lee, Tae Beom 167
Lee, Tae Hee 86, 174, 175
Lee, Wan-Sik 114
Lee, Won Jae 177
Lee, Woo Jung 67
Lee, Woohyung 121
Lee, Yoori 142
Lee, Youn Jae 38
Lee, Young 22
Lee, Young Hwan 90
Lee, Youngha 188
Lee, Young-Joo 168
Lee, Young-Sun 41, 62, 111, 116, 161
Lee, Youn-Jae 24
AUTHOR INDEX

Lee, Yun Bin 46, 51, 55, 62, 108, 150, 169
Lee, Yung Sang 19, 34, 36, 152
Lee, Yunhyeong 45
Lee-Kwon, Whaseon 13
Leem, Galam 46, 57
Li, Hua 55
Li, Ying 5
Li, Yueqi 39
Liang, T. Jake 23
Liao, Chien-Chang 43, 91
Lilly, Leslie 141
Lim, Jong Gu 136
Lim, Soo-Kyung 190
Lim, Tae Wan 163, 166
Lim, Won 26, 42, 101, 113, 118, 171, 153, 173
Lim, Young-Suk 11, 19, 24, 32, 34, 36, 37, 39, 147, 152, 197, 218, 323, 372
Lima, Joao A. C. 32
Lin, Billy 23
Lin, Chun-Yen 39
Lin, Shumei 39
Lin, Wenyu 103
Linaberry, M. 25
Liu, Lan 55
Liu, Lin 142
Liu, Xiao 103
Llovet, Josep M. 304
Lozada, Angelo 199
Lu, Sheng-Nan 39
Lu, Wei 39
Luo, Yan 39, 84, 147

McPhee, Fiona 39
Mederacke, Ingmar 52
Mehta, Rajiv 11, 32
Miller, Michael 147
Min, Hophil 76
Min, In Suk 93
Min, Jong Hwa 159
Minjuur, Boldbaatar 180
Miyoshi, Eiji 271, 384
Mizokami, Masashi 24
Mo, Hongmei 24, 147
Mo, L. 25
Mo, Ling 39
Mobashery, Niloufar 39, 147
Montealegre, Oscar Vargas 86
Moody, Stephanie 143
Moon, Deok-Bog 50, 59, 168, 183, 184, 367
Moon, Dong Gyu 31
Moon, Duk-Bok 122
Moon, Hee Seok 75
Moon, Hyuk 105, 149, 167
Moon, Hyuk Jin 96, 105
Moon, In Young 133
Moon, Jeong Seop 159
Moon, Keon Woong 31
Moon, Young Soo 102
Moreno, Christophe 3
Moser, Catherine D. 5
Mukazhanov, Adilbek 150, 169
Müllhaupt, Beat 141
Munkhdeemberel, S. 144
Munkh-Orshikh, Dashchirev 144, 156
Muratova, Zhansaya 169
Mushtaq, Kamran 171, 172, 175
Musin, Nadiar 181
Mustafinov, Dulat 176
Mutimer, David 147
Myltykbai, Rysmakanov 174
Myung, Dae-Seong 114

Maharjan, Pooja 188
Mangia, Alessandra 3
Mannalithara, Ajitha 26
Manns, Michael 142, 147
Mao, Xiao Wen 53
Marcellin, Patrick 11
Marlen, Doskali 174
Mashek, Douglas G. 277, 383
Massetto, Benedetta 11, 32, 35
Mauss, Stefan 142
Mazzotta, Francesco 3
McHutchison, John G 3, 11, 32, 141, 142, 147
McNally, John 3
McPhee, F. 27

N

N.M., Mussin 193
Na, Gun Hyung 6, 186
Na, Juri 13
Na, Seong Kyun 107, 127
Nah, Yang Won 66
Nakajima, Sanae 377
Nam, Byung Ho 108, 158, 159

www.theliverweek.org 399
<table>
<thead>
<tr>
<th>N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nam, Hee Chul</td>
<td>145</td>
</tr>
<tr>
<td>Nam, Ho Hyun</td>
<td>61, 64, 89</td>
</tr>
<tr>
<td>Nam, Ji Sun</td>
<td>74, 109</td>
</tr>
<tr>
<td>Nam, Joon Yeul</td>
<td>20, 44, 5, 109, 115, 117, 137</td>
</tr>
<tr>
<td>Nam, Soon Woo</td>
<td>112, 115, 119</td>
</tr>
<tr>
<td>Natha, Macky</td>
<td>3, 142</td>
</tr>
<tr>
<td>Nirajan, Shrestha</td>
<td>196</td>
</tr>
<tr>
<td>Niu, Junqi</td>
<td>39</td>
</tr>
<tr>
<td>Noh, Choong-Kyun</td>
<td>110</td>
</tr>
<tr>
<td>Noh, Ji Hyun</td>
<td>165</td>
</tr>
<tr>
<td>NS, Shulman</td>
<td>146</td>
</tr>
<tr>
<td>Nugroho, Adianto</td>
<td>157</td>
</tr>
<tr>
<td>Nuri</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Park, Choong Kee</td>
<td>87, 91, 164, 143, 192</td>
</tr>
<tr>
<td>Park, Chung-Hwa</td>
<td>22</td>
</tr>
<tr>
<td>Park, Dong Jun</td>
<td>83</td>
</tr>
<tr>
<td>Park, Eui Ju</td>
<td>127</td>
</tr>
<tr>
<td>Park, Eun Taek</td>
<td>38</td>
</tr>
<tr>
<td>Park, Eun-Sook</td>
<td>133</td>
</tr>
<tr>
<td>Park, Gil-Chun</td>
<td>50, 59, 122, 183, 184, 367</td>
</tr>
<tr>
<td>Park, Han Seul</td>
<td>63, 81</td>
</tr>
<tr>
<td>Park, Hye-Jung</td>
<td>147</td>
</tr>
<tr>
<td>Park, Hyeong Min</td>
<td>64</td>
</tr>
<tr>
<td>Park, Hyung Woo</td>
<td>66</td>
</tr>
<tr>
<td>Park, Hyung-Doo</td>
<td>32</td>
</tr>
<tr>
<td>Park, II Young</td>
<td>162, 186</td>
</tr>
<tr>
<td>Park, In-Yang</td>
<td>22</td>
</tr>
<tr>
<td>Park, Jae Ho</td>
<td>21, 94, 95, 96, 100, 137</td>
</tr>
<tr>
<td>Park, Ji Hee</td>
<td>159</td>
</tr>
<tr>
<td>Park, Ji Hye</td>
<td>140</td>
</tr>
<tr>
<td>Park, Ji Won</td>
<td>87, 91, 143, 164, 192</td>
</tr>
<tr>
<td>Park, Ji Yeon</td>
<td>339</td>
</tr>
<tr>
<td>Park, Ji Young</td>
<td>88</td>
</tr>
<tr>
<td>Park, Jiae</td>
<td>195</td>
</tr>
<tr>
<td>Park, Jihye</td>
<td>96</td>
</tr>
<tr>
<td>Park, Jin Young</td>
<td>131, 327</td>
</tr>
<tr>
<td>Park, Jin-hong</td>
<td>161</td>
</tr>
<tr>
<td>Park, Jong Ha</td>
<td>102</td>
</tr>
<tr>
<td>Park, Jun Gi</td>
<td>71</td>
</tr>
<tr>
<td>Park, Jun Yong</td>
<td>11, 20, 29, 36, 37, 46, 57, 71, 96, 99, 140, 148, 159, 162, 165, 168, 173, 196, 198, 199</td>
</tr>
<tr>
<td>Park, Jun Young</td>
<td>81</td>
</tr>
<tr>
<td>Park, Jung Ho</td>
<td>65</td>
</tr>
<tr>
<td>Park, Kyu Sang</td>
<td>21, 60, 81, 94, 95, 95, 100, 137</td>
</tr>
<tr>
<td>Park, Min Ji</td>
<td>174, 175</td>
</tr>
<tr>
<td>Park, Min Young</td>
<td>48</td>
</tr>
<tr>
<td>Park, Min-Su</td>
<td>132, 151</td>
</tr>
<tr>
<td>Park, Na Ri</td>
<td>104, 129</td>
</tr>
<tr>
<td>Park, Neung Hwa</td>
<td>13, 21, 94, 95, 96, 100, 128, 137</td>
</tr>
<tr>
<td>Park, Pyong-Jae</td>
<td>163, 166</td>
</tr>
<tr>
<td>Park, Sang Hoon</td>
<td>35, 86, 87, 143, 164, 192, 272</td>
</tr>
<tr>
<td>Park, Sang Jong</td>
<td>23, 30, 94, 104, 139</td>
</tr>
<tr>
<td>Park, Sang-Joon</td>
<td>58</td>
</tr>
<tr>
<td>Park, Sang Jung</td>
<td>21, 45, 67, 77, 87, 88, 95, 133</td>
</tr>
<tr>
<td>Park, Seong Jae</td>
<td>64</td>
</tr>
<tr>
<td>Park, Seong Eun</td>
<td>88</td>
</tr>
<tr>
<td>Park, Seung Ha</td>
<td>102</td>
</tr>
<tr>
<td>Name</td>
<td>Pages</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Park, Seung Woon</td>
<td>21, 45, 67, 77, 87, 88, 95, 133</td>
</tr>
<tr>
<td>Park, So Hyun</td>
<td>110</td>
</tr>
<tr>
<td>Park, Soo Young</td>
<td>34, 42, 71, 198</td>
</tr>
<tr>
<td>Park, Soohyun</td>
<td>129</td>
</tr>
<tr>
<td>Park, Sooeye</td>
<td>133</td>
</tr>
<tr>
<td>Park, Soyung</td>
<td>52, 153, 154, 154, 160</td>
</tr>
<tr>
<td>Park, Su A</td>
<td>69, 129</td>
</tr>
<tr>
<td>Park, Su Hyun</td>
<td>172</td>
</tr>
<tr>
<td>Park, Su-Hyung</td>
<td>3, 298</td>
</tr>
<tr>
<td>Park, Sun Seob</td>
<td>108</td>
</tr>
<tr>
<td>Park, Suyeon</td>
<td>58,</td>
</tr>
<tr>
<td>Park, Taesung</td>
<td>76, 161</td>
</tr>
<tr>
<td>Park, Yangsoo</td>
<td>152</td>
</tr>
<tr>
<td>Park, Young Hee</td>
<td>76</td>
</tr>
<tr>
<td>Park, Young Min</td>
<td>23, 30, 94, 104, 139</td>
</tr>
<tr>
<td>Park, Young Mok</td>
<td>167</td>
</tr>
<tr>
<td>Park, Young Nyun</td>
<td>29</td>
</tr>
<tr>
<td>Peck-Radosavljevic, Marcus</td>
<td>4, 141, 142</td>
</tr>
<tr>
<td>Pelemis, Mijomir</td>
<td>35</td>
</tr>
<tr>
<td>Peng, Cheng-Yuan</td>
<td>39, 147</td>
</tr>
<tr>
<td>Petersen, J.</td>
<td>4</td>
</tr>
<tr>
<td>Peterson, Jorg</td>
<td>142</td>
</tr>
<tr>
<td>Pilot-Matias, Tami</td>
<td>84</td>
</tr>
<tr>
<td>Pol, Stanislav</td>
<td>142</td>
</tr>
<tr>
<td>Prasad, Bhatt Nirmal</td>
<td>196</td>
</tr>
<tr>
<td>Prieto, Rei Joseph P.</td>
<td>155</td>
</tr>
<tr>
<td>Prokopenko, Yuriy</td>
<td>169</td>
</tr>
<tr>
<td>Ryu, Soo Hyun</td>
<td>159</td>
</tr>
<tr>
<td>S., Nancy Shulman</td>
<td>84</td>
</tr>
<tr>
<td>S., Patrick Kamath</td>
<td>361</td>
</tr>
<tr>
<td>Saeed, Waqar Khalid</td>
<td>61, 89, 92, 190</td>
</tr>
<tr>
<td>Sandzhari Abdullaev</td>
<td>4</td>
</tr>
<tr>
<td>Sang-Woo, Cha</td>
<td>114</td>
</tr>
<tr>
<td>Sarrazin, Christoph</td>
<td>84</td>
</tr>
<tr>
<td>Schnell, Greta</td>
<td>84</td>
</tr>
<tr>
<td>Schwabe, Christian</td>
<td>143</td>
</tr>
<tr>
<td>Schwabe, Robert F.</td>
<td>52</td>
</tr>
<tr>
<td>Seo, Kwang Il</td>
<td>22, 38, 57, 68</td>
</tr>
<tr>
<td>Seo, Seung Young</td>
<td>93, 170</td>
</tr>
<tr>
<td>Seo, Sooin</td>
<td>48</td>
</tr>
<tr>
<td>Seo, Yeon Seok</td>
<td>11, 21, 35, 41, 42, 45, 62, 67, 77, 87, 88, 95, 107, 111, 116, 133, 161</td>
</tr>
<tr>
<td>Seok, Jin</td>
<td>82</td>
</tr>
<tr>
<td>Seong, Donghyeong</td>
<td>32</td>
</tr>
<tr>
<td>Seoul Liver Group</td>
<td>107</td>
</tr>
<tr>
<td>Seounghyun, Kim</td>
<td>49</td>
</tr>
<tr>
<td>Seto, Wai Kay</td>
<td>11, 32</td>
</tr>
<tr>
<td>Shafran, Stephen D.</td>
<td>3</td>
</tr>
<tr>
<td>Shagdarsuren, M.</td>
<td>156</td>
</tr>
<tr>
<td>Shahzad, Ahmed</td>
<td>171, 172</td>
</tr>
<tr>
<td>Sharmenov, Abylaikhan</td>
<td>120</td>
</tr>
<tr>
<td>Shih, Chun-Chuan</td>
<td>91</td>
</tr>
<tr>
<td>Shih, Jae-Jun</td>
<td>52, 153, 154, 160</td>
</tr>
<tr>
<td>Shih, Ju Hyun</td>
<td>19, 36</td>
</tr>
<tr>
<td>Shih, Young Sup</td>
<td>110</td>
</tr>
<tr>
<td>Shin, Dae Kyu</td>
<td>169</td>
</tr>
<tr>
<td>Shin, Dong Hee</td>
<td>136</td>
</tr>
<tr>
<td>Shin, Eui-Cheol</td>
<td>3, 61</td>
</tr>
<tr>
<td>Shin, Hae Jin</td>
<td>130, 61, 75, 139</td>
</tr>
<tr>
<td>Shin, Hae-Young</td>
<td>91</td>
</tr>
<tr>
<td>Shin, Hyun Deck</td>
<td>101</td>
</tr>
<tr>
<td>Shin, Ik Sang</td>
<td>93</td>
</tr>
<tr>
<td>Shin, Jung Eun</td>
<td>101</td>
</tr>
<tr>
<td>Shin, Jung Woo</td>
<td>21, 94, 95, 96, 100, 128, 137</td>
</tr>
<tr>
<td>Shin, Seo Hyun</td>
<td>172</td>
</tr>
<tr>
<td>Shin, Seung Kak</td>
<td>98, 110, 168</td>
</tr>
<tr>
<td>Shin, Su Rin</td>
<td>143</td>
</tr>
<tr>
<td>Shin, Suk Pyo</td>
<td>169</td>
</tr>
<tr>
<td>Shin, Sun Young</td>
<td>138, 169</td>
</tr>
<tr>
<td>Shin, Sung Jae</td>
<td>74, 106</td>
</tr>
<tr>
<td>Shin, Sung Wook</td>
<td>112</td>
</tr>
<tr>
<td>Shin, Won Chang</td>
<td>88</td>
</tr>
</tbody>
</table>
Shin, Young Min
21, 94, 95, 96, 100, 137
Shin, Yu Ri
112, 115, 119
Shrestha, Nirajan
189
Shrestha, Rojeet
189
Silva, Marta
37
Sim, Heewoo
133
Sinn, Dong Hyun
267
Sinn, Dong Hyun
285
Sinn, Dong Hyun
5, 20, 32, 33, 44, 72, 83, 102,
112, 118, 136, 154, 155
Smagulov, Aibolat
174
Sohn, Areum
76
Sohn, Jong Hee
45
Sohn, Joo Hyun
12, 29, 56, 61, 64, 89, 189, 190
Sohn, Kyoung Min
92
Sohn, Won
94, 129, 139
Son, Sunyoung
338
Son, Won
23, 30, 104
Song, Byung-Cheol
177
Song, Do Seon
31, 44, 102, 162
Song, DongBeom
196
Song, Gi-Won
50, 59, 122, 152, 183, 184, 367
Song, Hyun Jin
195
Song, Il Han
101
Song, Jeong Eun
20, 99
Song, Ji-Ye
150
Song, Ki Jun
140
Song, Kijun
36
Song, Kyung Ho
174, 175
Song, Myeong Jun
36, 145, 162, 170, 191
Song, Sanghee
47, 182, 183, 184, 337
Song, Seung Hwan
48, 49, 50, 119, 122
Song, Tae-Jin
164, 194
Song, Young Bin
32
Soo, Keun Ahn
185
Sosorbaram, Ariunaa,
144
Spatayev, Zhanat
150
Spengler, U.
4
Sporea, Ioan
35
Stedman, Catherine
143
Stepanova, Tatjana
11
Subramanian, G Mani
11, 32
Subramanian, Mani
35
Sudimina, Dahal
196
Sugioka, Atsushi
377
Suh, Dong Jin
36
Suh, Jae Hee
13
Suh, Jeong Il
34, 71, 187
Suh, Kyung-Suk
6, 14, 47, 48, 64, 75, 111, 115,
127, 157, 178, 179, 180, 181,
182, 183, 184, 185, 337, 378
Suh, Sang Jun
21, 35, 41, 42, 45, 62, 67, 87, 88,
107, 111, 116, 139, 161, 162
Suh, Suk-Won
157, 178, 179, 180, 182, 183
Suk, Ki Tae
42, 45, 52, 67, 87, 143, 164
Sulkowski, Mark
229, 351
Sulkowski, Mark S.
3, 28, 84
Sultanaliyev, Tokan
169
Sultangereev, Erlan
193
Sultnaliyev, Tokan
120, 178, 191
Sumo, Marco
179
Sun, Eun Jang
72
Sung, Jae Kyu
75
Sung, Pil Soo
3, 22, 57, 61, 68, 163
Sunita, Ranabhat
132
Sup, Yoon Dong
165
Suzuki, Y.
27
Svarovskaia, Evgenia
3, 147

Taguba, Aubrey Q.
93
Tak, Won Young
11, 24, 32, 34, 71, 198, 329
Tan, Seng
197, 198
Tanahashi, Yoshinao
377
Teh, Catherine
199
Terrault, Norah
141
Tey, Sze Keong
53
The Korea Central
14
Cancer Registry
14
The Korean Liver
14
Cancer Study Group
11
The SOUL Study Group
Department of Internal Medicine
Timbol, Aeden Bernice G.
158
TM, Welzel
146
Torbeyns, Anne
39
Towner, William J.
3
Toyota, J.
27
Tran, Tram T.
3
Treitel, M.
25
Treitel, Michelle
39
Trinh, Roger
84
Tripathi, Rakesh
84
Tsai, Naoky
142
Tsang, Tak Yin Owen
32
Tse, Edith Yuk Ting
53
Tsendure, Munkhbaatar
132
U
U.T., Aidarkhan 193
Udompap, Prowpanga 26
Um, Soon Ho 21, 35, 42, 45, 67, 77, 88, 87, 95, 107, 133
Um, Yu Jin 52, 153, 154, 160
Undram, L. 144
Uyama, Ichiro 377
Uyanga, Naran 132

V
V, Isakov 146
Valenti, Luca 275, 385
Valero, Gabriel 168
Valk, M. van der 4
Vargas, Hugo 141
Vazquez, V. 25
Velasco, Mariel Dianne S. 93
Vera, Ramon L. de 155
Villa, Erica 346
Villamayor, Margaret Elaine J. 93

W
W, Xie 146
Wang, Hee Jung 74, 110, 120, 122, 131
Wang, Joon Ho 136
Wei, L. 25, 27
Wei, Lai 39
Wei, Mao 74, 120
Weiland, O. 4
Welzel, T.M. 4
Willems, Bernard 141
Won, Hae Lee 182
Won, Jae-Kyung 14
Won, Je Hwan 109
Won, Juhee 133
Won, Yoo Dong 160
Wong, Florence 35, 245, 355
Woo, Hyun Young 26, 34, 113, 118, 171

X
Xie, Q. 27
Xie, Qing 39
Xie, Wen 39
Xie, Yan 84
Xu, Min 39

Y
Yam, Judy Wai Ping 53
Yang, Hyun 145
Yang, Jae do 66, 175
Yang, Jenny C. 24, 28
Yang, Jin Mo 31
Yang, Kwang Ho 167
Yang, Kyung-Sook 68
Yang, Se Ra 172
Yang, Seok Jeong 69
Yang, Sien-Sing 131
Yang, Sung Yeun 102
Yang, Yong-Feng 39
Yasay, Eric B. 158
Yeh, Ming-Lun 149
Yeo, Injun 161
Yeo, Se Hwan 187
Yeo, Wook Hyun 88
Yeom, Seok Cheon 128, 134
Yeon, Jong Eun 21, 35, 41, 45, 62, 67, 87, 88, 107, 111, 116, 161, 211
Yerbol, Dzhussubaliev 191
Yesmembetov, Kakhman 85, 169, 176, 178
Yeum, Seok Chun 160
Ye, Byoung-Kee 32
Yi, Nam-Joon 6, 14, 47, 48, 64, 75, 111, 115, 127, 157, 178, 179, 180, 181, 182, 183, 184, 185, 337, 365
Yim, Hyung Joon 11, 21, 23, 24, 35, 41, 42, 45, 62, 67, 87, 88, 107, 111, 116, 139, 161, 162
Yim, Sun Young 42, 95
Yin, Philip D 39
Yoo, Byung Moo 106
Yoo, Byung-chul 34, 98, 135
Yoo, Jeong-Ju 47, 12, 13, 38, 46, 51, 55, 56, 70, 76, 107, 161
Yoo, Jung-Ju 117
Yoo, Ki Dong 31
Yoo, Sun Hong 23, 30, 94, 104, 139
Yoo, Sunhoo 108, 159
Yoo, Taekyeong 188
Yoo, Yang Jae 41, 62, 111, 116, 161
Yoon, Chang Jin 152
<table>
<thead>
<tr>
<th>Author Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoon, Eileen L.</td>
<td>44, 88, 98, 102</td>
</tr>
<tr>
<td>Yoon, Jae Hyun</td>
<td>106</td>
</tr>
<tr>
<td>Yoon, Jai Hoon</td>
<td>45</td>
</tr>
<tr>
<td>Yoon, Jung-Hwan</td>
<td>5, 13, 14, 20, 33, 42, 44, 46, 51, 54, 55, 64, 73, 75, 76, 103, 107, 109, 111, 115, 117, 137, 161</td>
</tr>
<tr>
<td>Yoon, Ki Tae</td>
<td>11,26, 32, 102, 113, 118, 148, 171, 263</td>
</tr>
<tr>
<td>Yoon, Kwon-Ha</td>
<td>90</td>
</tr>
<tr>
<td>Yoon, Kyung Chul</td>
<td>6, 14, 47, 127, 178, 182, 183, 184, 185, 178, 179, 180, 182, 337</td>
</tr>
<tr>
<td>Yoon, Sam-Youl</td>
<td>164, 194</td>
</tr>
<tr>
<td>Yoon, Sang Min</td>
<td>161</td>
</tr>
<tr>
<td>Yoon, Seung Kew</td>
<td>19, 22, 24, 26, 36, 57, 68, 83, 90, 104, 128, 129, 134, 163, 191</td>
</tr>
<tr>
<td>Yoon, Won Jae</td>
<td>159</td>
</tr>
<tr>
<td>Yoon, Young Chul</td>
<td>112, 119</td>
</tr>
<tr>
<td>Yoshida, Eric</td>
<td>3</td>
</tr>
<tr>
<td>Yoshida, Eric M.</td>
<td>141</td>
</tr>
<tr>
<td>Yoshimitsu, Kengo</td>
<td>223</td>
</tr>
<tr>
<td>Yotsuyanagi, Hiroshi</td>
<td>198</td>
</tr>
<tr>
<td>You, Chan Ran</td>
<td>90</td>
</tr>
<tr>
<td>You, Tae</td>
<td>181</td>
</tr>
<tr>
<td>You, Young Kyong</td>
<td>6, 186</td>
</tr>
<tr>
<td>Youn, Hyewon</td>
<td>13</td>
</tr>
<tr>
<td>Youn, Jin</td>
<td>142, 147</td>
</tr>
<tr>
<td>Youn, Sung Hee</td>
<td>192</td>
</tr>
<tr>
<td>Younes, Ziad</td>
<td>143</td>
</tr>
<tr>
<td>Young, Do Kim</td>
<td>173</td>
</tr>
<tr>
<td>Younossi, Zobair M.</td>
<td>37, 197</td>
</tr>
<tr>
<td>Yu, Eun Sil</td>
<td>152, 168</td>
</tr>
<tr>
<td>Yu, Goung-Ran</td>
<td>54,55</td>
</tr>
<tr>
<td>Yu, Hee Chul</td>
<td>66, 175</td>
</tr>
<tr>
<td>Yu, Je-Wook</td>
<td>210</td>
</tr>
<tr>
<td>Yu, Jung Hwan</td>
<td>85, 99</td>
</tr>
<tr>
<td>Yu, M.L.</td>
<td>27</td>
</tr>
<tr>
<td>Yu, Ming Lung</td>
<td>37, 147, 149</td>
</tr>
<tr>
<td>Yu, Su Jong</td>
<td>5, 13, 14, 20, 44, 46, 51, 54, 55, 73, 75, 76, 103, 107, 109, 111, 115, 117, 137, 161</td>
</tr>
<tr>
<td>Yu, Young Dong</td>
<td>133</td>
</tr>
<tr>
<td>Yu, Yun Suk</td>
<td>131</td>
</tr>
<tr>
<td>Yuk, Hyung Bin</td>
<td>174, 175</td>
</tr>
<tr>
<td>Yun, Byung Chul</td>
<td>38</td>
</tr>
<tr>
<td>Yun, Chohee</td>
<td>142, 147</td>
</tr>
<tr>
<td>Yun, Gee Young</td>
<td>75</td>
</tr>
<tr>
<td>Yun, Hyeon Jeong</td>
<td>191</td>
</tr>
<tr>
<td>Yun, Ki Jung</td>
<td>90</td>
</tr>
<tr>
<td>Yun, Young-In</td>
<td>183</td>
</tr>
<tr>
<td>Yurdidin, Cihan</td>
<td>35</td>
</tr>
</tbody>
</table>

**Z**

<table>
<thead>
<tr>
<th>Author Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zakria, Muhammad</td>
<td>194</td>
</tr>
<tr>
<td>Zeuzem, Stefan</td>
<td>3, 4</td>
</tr>
<tr>
<td>Zha, Jiuhong</td>
<td>39, 147</td>
</tr>
<tr>
<td>Zhaksulyk, Doskaliyev</td>
<td>174</td>
</tr>
<tr>
<td>Zhang, Jun</td>
<td>54</td>
</tr>
<tr>
<td>Zhang, Mingxiang</td>
<td>39</td>
</tr>
<tr>
<td>Zhang, Xinyan</td>
<td>39</td>
</tr>
<tr>
<td>Zhao, Y.</td>
<td>4</td>
</tr>
<tr>
<td>Zharkimbekov, Bakhyt</td>
<td>127, 169</td>
</tr>
<tr>
<td>Zhenalayev, Damir</td>
<td>176</td>
</tr>
<tr>
<td>Zhexembayev, Asan</td>
<td>150, 169</td>
</tr>
<tr>
<td>Zhou, N.</td>
<td>27</td>
</tr>
<tr>
<td>Zhu, Andrew X.</td>
<td>297</td>
</tr>
<tr>
<td>Zhu, Yanni</td>
<td>3</td>
</tr>
</tbody>
</table>
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본 강의록의 내용은 저작권법의 보호를 받으며 무단 복제를 금지함.
In advanced liver disease related to chronic hepatitis B infection,

Cirrhosis was previously thought to be irreversible,

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The 5-year VIREAD histology data provides the evidence that 0% resistance and long-term suppression of HBV can lead to significant regression of fibrosis and reversal of cirrhosis in substantial proportion of treated patients.
THE LONG-AWAITED RESPONSE IN THE TREATMENT OF HEPATITIS C

Introducing DAKLINZA and SUNVEPRA, in Korea, in the first all-oral, interferon- and ribavirin-free regimen that cures* hepatitis C in a majority of your patients.1,2

* Long-term follow-up studies have shown that an SVR corresponds to a durable cure of HCV infection in more than 90% of cases with interferon-based regimen.3


DAKLINZA Tablet (daclatasvir) [Active Ingredient] Daclatasvir tablet contains 60 mg of daclatasvir hydrochloride. — DAQINZA Tablet [Drug Product Description] Light green, rectangular, tapered tablets marked with a circled trademark symbol. The treatment of chronic hepatitis C virus (HCV) or genotype 1b infection in adults with compensated liver disease (including cirrhosis) in combination with other medicines. (Dosage and Administration) 1. Recommended Dosage The recommended dose of this drug for the treatment of chronic HCV genotype 1 infection is 60 mg, taken once daily, orally, with or without food. In combination with SUNVEPRA 100 mg daily for 24 weeks. 2. Dose modification and Temporary Interruption Once treatment is started, dose modification of this drug is not recommended. There is no recommended procedure for dose modification of this drug in the regimen. Treatment interruption should be avoided; however, if treatment interruption is necessary because of adverse reactions, the drug must not be given as monotherapy. Patients should be instructed that if they miss a dose of the drug, the dose should be taken as soon as possible. If more than 12 hours of the scheduled dose time have elapsed, the dose should be skipped and the next dose taken at the appropriate time. 3. Discontinuation Regular monitoring of serum lipase and (HCV RNA) levels during treatment. Patients with an inadequate virologic response during treatment are unlikely to achieve sustained virologic response (SVR) and may develop lipase elevation and/or sudden death. Discontinue the anti-HCV treatment regimen for patients experiencing persistent elevation of lipase greater than 3 times the ULN, increase in HCV RNA (final value greater than baseline value) (PLC), and then confirmed by having detectable HCV RNA (PLC) during treatment. (Warnings and Precautions) 1. Discontinuation: This drug is contraindicated in patients with previously automated hepatitis C virus (HCV) RNA levels during treatment. Patients with an inadequate virologic response during treatment are unlikely to achieve sustained virologic response (SVR) and may develop lipase elevation and/or sudden death. Discontinue the anti-HCV treatment regimen for patients experiencing persistent elevation of lipase greater than 3 times the ULN, increase in HCV RNA (final value greater than baseline value) (PLC), and then confirmed by having detectable HCV RNA (PLC) during treatment. (Warnings and Precautions) 1. Discontinuation: This drug is contraindicated in patients with previously automated hepatitis C virus (HCV) RNA levels during treatment. Patients with an inadequate virologic response during treatment are unlikely to achieve sustained virologic response (SVR) and may develop lipase elevation and/or sudden death. 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[indications and usage] SOVALDI is indicated in combination with other medicinal products for the treatment of genotype 1, 2, 3, 4, 5, and 6 HCV infected patients. SOVALDI is not recommended for patients with AIDS, liver cirrhosis, or severe comorbidities.

- **DOSAGE AND ADMINISTRATION**: The recommended dose is one 400 mg tablet, taken once daily with or without food. SOVALDI should be used in combination with other medicinal products.

- **ADVERSE REACTIONS**: This includes nausea, vomiting, headache, diarrhea, and fatigue.

- **DRUG INTERACTIONS**: SOVALDI should not be used in combination with rifampin or rifabutin.

**References**:


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2. 알부민 합성저하(간경변증 등)에 의한 저알부민혈증
3. 출혈성 축
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- Cytoprotective effects
- Immunomodulatory effects
- Stimulation of bile secretion

**Composition**
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**Indication/Dosage and administration**
- 100mg Tab.: - Adjuvant therapy for liver disease due to insufficient bile secretion and biliary disease (gallbladder and biliary tract)
  - Improvement of hepatic function in chronic liver disease
  - Sequela of excision of small intestine and indigestion due to inflammatory small intestinal disease
  - Gallstones
  - For adults, usually 50–100mg t.i.d., Gallstones: 200mg t.i.d.

- 200mg Tab.: - Gallstones: 200–250mg t.i.d.
  - Primary biliary cirrhosis (PBC): 200–300mg t.i.d.

- 300mg Tab.: - Primary biliary cirrhosis (PBC): 300mg t.i.d.

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- For peripheral arterial occlusive disease
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With Nexavar® you can optimize outcomes for your patients with HCC

* LRT= Locoregional therapies  
HCC= Hepatocellular carcinoma

Product Name NEXAVAR® Tablet 200 mg
Composition Each tablet contains sorafenib tosylate (274mg) equivalent to 200mg of sorafenib
Indications 1) Hepatocellular carcinoma 2) Patients with advanced renal cell carcinoma who have failed prior cytokine 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.

Contraindications 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=61), 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/

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3. Increasing in mitochondrial DNA copy number
4. Activating immune cells in the liver to release cytokines (IL, TGF, TNF)
ENGINEERED FOR A LIFETIME OF CONSISTENT CONTROL

- Variability in calcineurin inhibitor exposure can result in reduced renal function or graft life.\(^1\)\(^-\)\(^3\)

- Higher intrapatient variability in PROGRAF® (tacrolimus) exposure was associated with an increased risk of graft failure beyond 12 months post-transplant (P=0.003)\(^4\)

- Prolonged-release ADVAGRAF has been engineered to deliver a lifetime of consistent, predictable control of tacrolimus exposure\(^5\)

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