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Evidence and Consensus on HCC Management

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Abstracts

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State-of-the-Art Lectures

Speaker's Curriculum Vitae

Name Philip J. Johnson, MD, FRCP
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Professor Johnson qualified in medicine at the University of Manchester and subsequently held posts as Senior House Officer at four major London Post-graduate Centres, including the Royal Marsden Hospital, before moving to the Liver Unit at King's College Hospital, London. Here he gained initial training in hepatology, and an introduction to clinical and laboratory research in the field of liver and pancreatic cancer.

After a two year appointment at Manchester Royal Infirmary in General Medicine and Gastroenterology he returned to the Liver Unit at King's College Hospital, London (now The Institute of Liver Studies), as Senior Lecturer and Assistant Director, in charge of the newly built extension to the Unit, the Sheikh Zaid Centre.

From London he moved to The Chinese University of Hong Kong where he was Professor of Clinical Oncology and Head of Department. He commissioned a new Cancer Centre (the Sir Y.K. Pao Centre for Cancer) involving over 300 researchers and built up the Comprehensive Clinical Trials Unit.

Professor Johnson returned to the UK in 2002 to the Chair of Oncology and Translational Research at the School of Cancer Sciences, University of Birmingham where he was also Director of the Cancer Research UK Clinical Trials Unit, one of the largest of its type in the United Kingdom.

In 2012 he was appointed to the Chair of Translational Oncology at the University of Liverpool and Clatterbridge Cancer Centre and is Clinical Academic Lead for Cancer at Liverpool Health Partners.

His main clinical interest is in hepatobiliary cancer and biomarker discovery in the setting of clinical trials. He has over 400 publications including original papers, textbook chapters and reviews.

SL1

Regional Variation in HCC Survival – Impact of Surveillance and Assessment of HCC-Associated Liver Dysfunction

Philip J. Johnson

University of Liverpool, UK

International guidelines all support surveillance for early detection of HCC but, in the absence of clear evidence that such surveillance decreases disease specific mortality, support from funders is often lacking. The requisite supportive evidence-base in the form of prospective randomised studies is absent and unlikely to be forthcoming.

In an international collaboration we have compared, using patient level data (PLD, n = 6,485), several large cohorts of HCC patients from different regions of the world. Here we focus on a comparison between two of the regions, both with sophisticated healthcare systems. One (Japan) has a long-standing intensive, nationally-funded HCC surveillance programme whereas Hong Kong has no such formal programme. In Japan the majority (77.6%) of cases were detected by surveillance whereas in Hong Kong less than 20% of cases were detected pre-symptomatically. Median survival was, over a recent comparable time period, 52 months in Japan (having increased from <3 months before initiation of the surveillance programme) and 7.2 months in Hong Kong; this survival advantage persisted after allowance for lead-time bias. Sixty two percent of Japanese patients had early disease at diagnosis and 63% received curative treatment. The comparable figures for Hong Kong were 8 and 16% respectively. Such wide differences could not be accounted for by disease aetiology. The variation in survival is largely accounted for by stage at diagnosis, which in turn relates to the intensity of surveillance programmes and the consequent variation in curative therapeutic options.

The ALBI score is a recently published model (PLD from 6,410 patients), based on only serum **albumin** and **bilirubin** that purports to assess liver (dys) function in patients with HCC. Supporting the validity of ALBI (graded as 1 (best) to 3 (worst)) there is a strong correlation with ICG clearance (n = 2,190), ALBI grade has no influence on survival after liver transplantation (n = 292) and ALBI clearly stratifies survival in patients with chronic liver disease (without HCC). Within HCC patients with Child-Pugh (C-P) grade A, ALBI stratified patients with early disease (n = 2,641) and intermediate stage disease (n = 2,454) into two or three clear and non-overlapping groups with ALBI-1 patients surviving about twice as long as ALBI-2 patients. Similarly, in 1,132 Child-Pugh A patients receiving Sorafenib for advanced HCC median survival was 12.7 months in those with ALBI-1 and 7.2 months in those with ALBI-2. ALBI can sensitively monitor changes in liver function attributable to therapeutic interventions. Finally, serial ALBI estimation suggests that part of the increase in survival in Japan over recent years may be attributable to improvement in underlying liver function at diagnosis, at a time when the median tumour size at detection is no longer decreasing.

Speaker's Curriculum Vitae

Name Josep M. Llovet, MD
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Josep M. Llovet is **Professor of Research-ICREA** in the BCLC Group, Liver Unit, IDIBAPS-Hospital Clínic de Barcelona (Spain), **Director of the Liver Cancer Program and Full Professor of Medicine** at the Mount Sinai School of Medicine, New York University (USA), and **Professor** at Faculty of Medicine, University of Barcelona. Professor Llovet obtained his degree in Medicine and Surgery from the University of Barcelona in 1986 and his PhD from the Autonomous University of Barcelona in 1995.

Professor Llovet has been **President of the International Liver Cancer Association (ILCA)** and Chairman of the European Clinical Practice Guidelines of management of liver cancer (EASL-EORTC). He has published more than 220 articles in peer-reviewed journals such as *New England Journal of Medicine*, *Nature*, *Nature Genetics*, *Lancet*, *Cancer Cell*, *Journal Clinical Investigation*, *Journal of Clinical Oncology*, *Lancet Oncology*, *Gastroenterology* and *Hepatology* (total citations 33.629, total impact factor 2234; **h index 77**), more than 40 chapters of books, and has delivered more than 450 lectures. He is Senior Editor of *Clinical Cancer Research*. He is Director of the Official Master in Translational Medicine at the University of Barcelona.

During the last 20 years, Dr. Llovet received the AACR-Landon International Award (2009), the International Hans Popper award (2012), Premi Josep Trueta (2013) and is leading international projects with competitive funding from the European Commission (FP7-HEALTH, HEPTROMIC, 2010) and the US National Institute of Health (R01, 2008). Below, find described the scientific and managerial positions and the main scientific achievements obtained. He has contributed to advancing knowledge in the following areas:

Main Achievements

1. **Clinical classification of HCC:** with the acronym BCLC (Barcelona-Clínic Liver Cancer) classification, first published in Llovet, *Semin Liv Dis* 1999, and then further modified in Llovet, *Lancet* 2003; Llovet, *J Natl Can Inst*, 2008 and Forner, *Lancet* 2012. This classification has been adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.
2. **Establishment of sorafenib as standard of care** in patients with advanced HCC (Llovet, *New Engl J Med* 2008). This breakthrough achievement establishes sorafenib as first line treatment for advanced HCC, and represents the first identification of survival advantages with systemic treatments. Identified by *Nature Medicine* as the most cited paper in oncology 2008–2010. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.
3. **Molecular classification of HCC and intrahepatic cholangiocarcinoma:** A final proposal of a molecular classification of HCC and ICC is based on the results reported in different publications (Wurmbach, *Hepatology* 2007; Hoshida, *New Engl J Med*, 2008, Chiang, *Cancer Res*, 2008; Hoshida, *Cancer Res* 2009, Villanueva, *Gastroenterology* 2011; Sia, *Gastro* 2013, Hoshida, *Gastroenterology* 2013).
4. **Identification of drivers of oncogenesis as targets for therapies.** Several studies led to the identification of **mTOR pathway** [Villanueva *Gastroenterology*, 2008], **Ras pathway** (Newell, *J Hepatol* 2009), **EGFR pathway** (Keng, *Nature Biotech* 2009), **IGF pathway** ([Tovar, *J Hepatol*, 2011], **Wnt Pathway** (Lachenmeyer, *CCR* 2012), **Notch pathway** (Villanueva, *Gastroenterology* 2012), AEG (Yoo, *J Clin Invest* 2009). **miRNAs** (Viswanathan, *Nat Genetics* 2009, Toffanin, *Gastroenterology* 2011) and **FGF19** as drivers of hepatocarcinogenesis and potential targets for therapies. Regarding ICC, discovery of **FGFR2 fusions** and **ARAF** mutations as drivers of tumor progression.

Other Important Achievements

1. **Establishment of chemoembolization as standard of care** in patients with intermediate HCC. Evidence-based establishment through randomized controlled trials [Llovet, *Lancet* 2002] and meta-analysis [Llovet, *Hepatology* 2003] of chemoembolization as standard of care in patients with intermediate HCC. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.
2. **Guidelines of management of HCC:** Chair of EASL-EORTC Guidelines, 2012 (*J Hepatol*, 2012, *Eur J Cancer* 2012), and committee member of guidelines of EASL (2001). Leading author of AASLD guidelines for design of clinical trials in HCC (Llovet, *J Natl Cancer Institute*, 2008).
3. **Establishment of a molecular diagnosis of HCC:** Gene-set (3 genes) based diagnosis of HCC reported in Llovet, *Gastroenterology* 2006, and included in EASL-EORTC guidelines.

SL2-1

Design of Clinical Trials in Advanced HCC: Trial Enrichment and Stratification

Josep M. Llovet^{1–3,*}

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Hepatocellular carcinoma (HCC) is a major health problem. Since the SHARP data were published in 2007 [1], results of clinical studies testing new agents have been disappointing. None of the studies in adjuvant setting, intermediate stages and first and second-line advanced HCC trials have been positive [2]. Continuing the drug development process in the same manner as we have in the past is unlikely to yield significant improvements. Trials targeting all comers are still expected when testing drugs with broad mechanisms of action (multi kinase inhibitors, immunotherapy), but a more precise strategy is needed [2].

Recommendations on trial design are evolving in the HCC field [3–4]. Regarding end-points, overall survival is adequate not only for phase III studies, but also to interpret phase II data in first and second line. Time to progression (TTP) has been challenged as an end-point due to some disconnections between TTP and OS [2], although specific studies exploring this connection are still awaited. Trial enrichment might become an important tool for optimizing trial design in the years to come. Several drugs have granted approval based on enriched populations (i.e. vemurafenib in BRAF+ melanoma; crizotinib in ALK+ lung cancer). In HCC, few cases of enrichment are ongoing, such as refametinib in RAS+ cases, tivantinib in MET+ cases and Ramucirumab in patients with HCC and AFP >400 ng/ml [5]. Additional trials are planned, as those with FGFR4 inhibitors in patients with HCC and overexpression of FGF19, among others. Biomarkers for trial enrichment or stratification of patients are expected to improve the window of opportunity of novel drugs. In parallel, some studies have suggested that recommended stratification factors in first line trials (such as region, macrovascular invasion/extrahepatic spread, ECOG status) should be revisited in designing second-line studies. In these studies, macrovascular invasion [6] and type of tumor progression [7] should be also considered.

In conclusion, refinement of trial design based on understanding of tumor biology and clinical relevance is leading to changes in inclusion criteria (trial enrichment) and more personalized stratification factors. In order to consider all these factors, current guidelines recommend obtaining tumor biopsies in the setting of HCC research studies.

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Speaker's Curriculum Vitae

Name Andrew X. Zhu, MD, PhD
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Dr. Andrew X. Zhu is Director of Liver Cancer Research at Massachusetts General Hospital Cancer Center and an Associate Professor of Medicine at Harvard Medical School. The major focus of his research is to develop more effective therapies for hepatocellular carcinoma (HCC) and cholangiocarcinoma through phase I, II and III clinical trials. The second area of his research interests is directed at the development of novel circulating and imaging biomarkers for targeted therapeutics that have prognostic and/or predictive significance. The third area of his research is to define and characterize known or novel genetic mutations in HCC and cholangiocarcinoma and assess their potential correlation with clinical outcomes and as therapeutic targets.

As a widely published author, Dr. Zhu has served as a principle investigator in many clinical trials in HCC, cholangiocarcinoma and other gastrointestinal cancers. He is the invited reviewer for many medical journals and has lectured extensively on HCC and other gastrointestinal cancers. An internationally recognized leader in HCC and cholangiocarcinoma, he has led early efforts of developing several molecularly targeted agents in liver cancers and studying the predictive and surrogate circulating and imaging biomarkers. He is a founding board member of the International Liver Cancer Association, Fellow of American College of Physicians, and a member of the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research. Dr. Zhu serves on the Hepatobiliary Cancer committee of the National Comprehensive Cancer Network, the Grants Selection Committee of ASCO, and the Hepatobiliary Cancer Task Force of The NCI Gastrointestinal Cancer Steering Committee (GISC).

SL2-2

Cholangiocarcinoma: New Trends and Emerging Targets

Andrew X. Zhu

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Cholangiocarcinoma is a relatively rare malignancy that arises from the epithelial cells of the intrahepatic, perihilar and distal biliary tree. The incidence of intrahepatic cholangiocarcinoma (ICC) has been rising steadily for decades and molecular profiling studies suggest that it is likely greatly under-diagnosed. Majority of the patients present with locally advanced or metastatic disease. Despite treatment with the standard regimen of gemcitabine and cisplatin, prognosis remains dismal with a median survival of less than one year. The anatomical, pathological and molecular heterogeneity of cholangiocarcinoma presents with unique challenge for drug development. Recently, targeted and whole exome sequencing efforts have defined the landscape of mutations underlying these tumors and revealed ICC as having a completely unique genetic profile among all other epithelial malignancies. Importantly, a significant percentage of ICC harbors oncogenic driver mutations that may confer sensitivity to specific targeted therapies already in clinical development. With the potential for developing novel targeted therapies on the horizon, a greater focus on the recognition, diagnosis, and molecular profiling of cholangiocarcinoma is required to provide novel therapeutic options in this intractable disease.

Session 1 Prevention of HCC

Speaker's Curriculum Vitae

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In medical research career, Chun-Ying Wu received his M.D. degree from the National Taiwan University in 1991, M.P.H. degree from Harvard School of Public Health in 1993, and Ph.D. degree from National Taiwan University in 2007. Prof. Wu has positions as the Joint Appointment Researcher of National Institute of Cancer Research, and also Professor of Medicine at various universities, including the National Yang-Ming University, the National Chung-Hsing University, and the China Medical University. He is currently the Associate Editor-in-Chief of *Advances in Digestive Medicine (AIDM)*, Vice-Secretary General of both Gastroenterological Society of Taiwan (GEST) and Digestive Endoscopy Society of Taiwan (DEST), the Executive Council Board Member for Taiwan Liver Cancer Association (TLCA), and the Control Board Member of the Taiwan Evidence-based Medicine Association (TEBMA). Prof. Wu is also the President of the 2015 TLCA annual meeting.

His medical research interests focus on translational studies of digestive cancers. Prof. Wu used Taiwan's National Health Insurance Research Database, clinical research, *in vitro* studies and animal experiments to develop new tumor markers, risk prediction tools, nanobiochips, therapeutic agents, chemopreventive methods and nationwide health policies. He has published many articles in top ranking peer-reviewed journals such as *JAMA*, *J Clinical Oncology*, *Gastroenterology*, *Gut*, *Hepatology*, *Clin Gastroenterol Hepatol*, *Annals of Surgery*, *Clinical Cancer Research*, *Arthritis Rheumatology*, and *Radiology*, etc.

In addition to medical career, Prof. Wu is also very active in legal societies. He received his LL.B. degree from Tunghai University in 2000 and LL.M. degree from Harvard Law School in 2003. He has a position as Professor of Law in College of Law at the Tunghai University. He currently serves as the Committee Member of Medical Dispute Assessment Committee of Ministry of Health and Welfare (MHW), the Committee Member of Institute Review Board of the National Health Research Institutes (NHRI), and Vice President of the Society of Law and Medicine, Taiwan (SLMT). His legal research interests include medical malpractice litigation and biotechnology regulation. Prof. Wu has published four law textbooks, four chapters in law books, and many articles in peer-reviewed journals including *Taiwan Law Review*, *Internal Medical Journal*, *FT Law Review*, *Journal of New Perspective on Law*, etc.

Medical Research Interest: Translational research of digestive cancers

Legal Research Interest: Medical malpractice and biotechnology regulation

S1-1

Antiviral Therapy for HCC 2nd and 3rd Prevention

Chun-Ying Wu

Taichung Veterans General Hospital, National Yang-Ming University,
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Hepatocellular carcinoma (HCC) is the third common cause of cancer-related mortality worldwide with more than 745,000 deaths annually. Many risk factors contribute to the development of HCC, including hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease, and metabolic syndrome. Among these factors, HBV and HCV are the most frequent underlying causes of HCC and accounts for more than half of HCC cases. Higher HBV and HCV viral levels are associated with increased risk of HCC development and recurrence.

Antiviral therapy not only suppresses viral replication and attenuates liver diseases progression, but also plays a major role in HCC secondary and tertiary prevention. Our recent nationwide cohort study found antiviral therapy associated with significantly reduced risk of HCC development in HBV patients (7-year cumulative incidences of HCC: 7.32% in treated cohort vs. 22.7% in the untreated cohort). The adjusted hazards ratio (HR) was 0.37. This secondary prevention effect is especially found in younger patients, patients without cirrhosis, and without diabetes. Also based on a nationwide cohort study, we found nucleoside analogues associated with reduced risk of HBV-related HCC recurrence following liver resection (adjusted HR = 0.67; 6-year cumulative HCC recurrence rates: 45.6% and 54.6% for the treated and untreated cohorts, respectively). For HCV-related HCC, we found interferon plus ribavirin was associated with reduced recurrence risk after liver resection (adjusted HR = 0.64). The mortalities of HBV-, and HCV-related HCC were also reduced by antiviral therapy.

In conclusion, antiviral therapy is associated with a reduced risk of HCC development and recurrence. Further studies will be helpful to investigate the magnitude of this beneficial effect and to examine whether antiviral therapy should be used in all or only a subset of these HCC patients.

Speaker's Curriculum Vitae

Name Namiki Izumi, MD, PhD
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Namiki Izumi is Director of Department of Gastroenterology and Hepatology, Musashino Red-Cross Hospital and Clinical Professor, Tokyo Medical and Dental University.

He received his medical degree at the Tokyo Medical and Dental University in Japan. He served his residency in medicine and fellowship in the second department of Internal Medicine at the hospital of Tokyo Medical and Dental.

Namiki Izumi is an active board member of the Japanese Society of Hepatology, currently serving on the Guideline committee member of viral hepatitis and the social insurance committee as chairman.

In 2014, He served as the president for 50th anniversary meeting of Japan Society of Hepatology in Tokyo.

He is also an active board member of the Japanese Association for Liver Cancer, currently serving on the Guideline committee member of hepatocellular carcinoma.

He has served as Chief Investigator of study groups funded by Japanese Ministry of Health, Welfare and Labor (MHLW) for clinical study of viral hepatitis and hepatocellular carcinoma and data mining analysis for chronic hepatitis C.

He has an active practice and serves as a principal investigator on many important trials involving antiviral therapy for both hepatitis B and C.

Namiki Izumi has a special interest in chronic viral hepatitis and hepatocellular carcinoma, focusing on the epidemiology, natural history and antiviral therapies for these diseases.

S1-2

Prevention of HCC in HCV Infection; Interferon or DAA?

Namiki Izumi

Director of Department of Gastroenterology and Hepatology, Musashino Red-Cross Hospital and Clinical Professor, Tokyo Medical and Dental University, Tokyo, Japan

Hepatocellular carcinoma (HCC) has characteristic features of the coexistence of two life-threatening conditions, cancer and cirrhosis, and to improve of the prognosis of the patients with HCC is an urgent issue. To eradicate HCV has been progressed rapidly by direct acting anti-virals (DAA), however, the preventive effect of DAAs remains to be clarified. The most important predictive factors for the development even after achieving sustained virological response (SVR) are alfa-fetoprotein and alanine aminotransferase after SVR. In addition, the high rate of intrahepatic recurrence is a key feature which correlates with poor prognosis, and its prevention is an issue for urgent investigation. The long-term prognosis after surgical resection of HCC remains unsatisfactory compared to other common human cancers because of the high rate of recurrence and lack of effective adjuvant therapy.

Interferon was first shown to be effective for the prevention of recurrence by a randomized study using beta interferon. However, interferon did not affect overall prevention of HCC recurrence after resection or RFA but, if the HCV infection had been cured, interferon was effective for preventing the development of HCC and improving survival. Therefore, it is an important issue to clarify whether HCV eradication after curative treatment of HCC prevent the recurrence of HCC, or not. Biomarker to predict the recurrence should be examined.

Speaker's Curriculum Vitae

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Ji-Dong Jia studied medicine at Jining Institute of Medicine, and received his training on gastroenterology and a Master's degree at Lanzhou Medical College, and received his training on hepatology and a Doctor's degree at Capital Institute of Medicine, China. He finished his postdoctoral training on cell and molecular biology on liver fibrosis at Free University of Berlin, Germany.

He is the president of the International Association for the Study of Liver (IASL) and was president of the Asia-Pacific Association for the Study of the Liver (APASL, 2009–2010) and the Chinese Society of Hepatology (CSH, 2006–2012). He also serves or served as associated editor of *Journal of Gastroenterology and Hepatology*, *Hepatology International* and *Liver International*. He is member of editorial board of *Gut*, *Antiviral Therapy*, and *Journal of Digestive Diseases*.

As a clinical hepatologist with special interest on viral hepatitis and related cirrhosis and hepatocellular carcinoma, he has published widely in international peer review journals including *Hepatology* and *Journal of Hepatology*. He also makes a lot commitment to public health issues of viral hepatitis prevention and control. He is currently serves as the vice president of China Foundation for Hepatitis Prevention and Control (CFHPC) and council member of Coalition to Eliminate Viral Hepatitis in Asia-Pacific (CEVHAP).

S1-3

Prevention of HBV-Related HCC

Jidong Jia

Beijing Friendship Hospital, Capital Medical University, Beijing, China

Hepatocellular carcinoma (HCC) is among the top five most common malignant tumors and carries top 2 mortality among all malignancies. Hepatitis B virus (HBV) is a major cause of HCC worldwide and leading cause of HCC in Asian countries except Japan. For example, chronic HBV infection is causally associated with over 80% of HCC in China. In the last decade, a series of long-term, large scale cohort studies confirmed that the serum HBV DNA levels are strongly associated with the incidence of HCC. Therefore, HBV-related HCC could be prevented at three levels, namely, primary prevention of HBV infection with vaccination, secondary prevention of HCC occurrence with antiviral therapy among persons with chronic hepatitis B (CHB), and tertiary prevention of HCC mortality with antiviral therapy among persons with HCC.

Primary prevention of HBV infection with vaccination: Considering HBV infection is spread mainly through mother-to-infant (mostly perinatal) transmission and early childhood transmission in China, universal HBV vaccination in neonates and infants would be a very cost-effective way to control HBV infection. Studies from China mainland and Taiwan both show that universal infant HBV immunization could reduce the risk of HCC development in young age group.

Secondary prevention of HCC occurrence among persons with CHB: The primary goal of antiviral therapy is to prevent the disease progression to cirrhosis and HCC. Both randomized clinical trials and long-term cohort studies demonstrate that effective antiviral therapy could reduce but not completely eliminate the risk of HCC development in patients with CHB and cirrhosis.

Tertiary prevention of HCC recurrence with antiviral therapy in patients who already developed HCC: Numerous studies also show that serum HBV DNA levels are correlated with the progression and recurrence of HCC. Reports from Asia and other parts of the world demonstrate that antiviral therapy could reduce the progression and recurrence rate of HCC, thereby prolong the survival of the patients.

Speaker's Curriculum Vitae

Name Lai Wei
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Dr. Lai Wei is a hepatologist with thirty-two years' experience in hepatology clinical practice and research. Dr. Wei is currently the Director and Professor of Peking University Hepatology Institute at Peking University People's Hospital in Beijing, China. He is the leading-PI of Major Project for Infectious Diseases Control during the 10th and 11th Five-Year Plan Period and Key Clinical Research Program of Ministry of Health. He conducted 1200 hepatitis C patients cohort. Dr. Wei is member for a few of hepatitis C guidelines including KDIGO, APASL, China. He is the author of more than 50 peer-reviewed scientific publications.

S1-4

Control of HCV-Related HCC in China

Lai Wei

Peking University Peoples' Hospital

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with the majority of cases associated with persistent infection from hepatitis B virus (HBV) or hepatitis C virus (HCV).

The prevalence of HCV in China is estimated to be 2.2% with a range of 2.1% in Fujian province to 9.6% in Henan province, with an higher prevalence in injection drug users and hemodialysis patients.

Our team have reported a first country-wide survey with 1,012 HCV-infected patients from 28 university hospitals across China. Genotype 1b was the most common with overall prevalence of 56.8%, and it is the predominant genotype in the east (71.8%). The less common genotype 6 was found mainly in the south (20.4%) and the west (6.9%). The south displayed the greatest diversity of the HCV genotypes. The rs12979860 polymorphism near the human interleukin-28B (IL28B) gene is associated with interferon responsiveness. The IL28B-CC genotype, which is associated with favorable response to interferon and spontaneous HCV clearance, predominates in China with an overall prevalence of 84.1%.

The reported incidence of hepatitis C in China has increased >10-fold from 2003 to reach 219,110 cases in 2012. The reasons included better diagnosis, disease progression of the aging infected populations, as well as new infections.

Chinese government has paid more and more attention on the prevention, diagnosis and care of hepatitis C. We have got achievement as below:

- 1 Ministry of Health, People's Republic of China promulgated Blood Donation Law of the People's Republic of China in 1998. It emphasized blood donation without compensation and blood screening before donation. It significantly attributed the decline of prevalence of HCV infection among blood donors in recent years.
- 2 Chinese Preventive Medicine Association promulgated the guideline of control and prevention of hepatitis C transmission in hospitals in 2013. It Outlined policy aimed to increase protection of health care workers and to decrease transmission in hospitals.
- 3 Ministry of Health, People's Republic of China promulgated the health industry standard of the People's Republic of China-Screening and management of viral hepatitis C. This standard defined targeted populations that need screening for HCV, screening occasions and methods and management of HCV patients.
- 4 In some patients, antiviral treatment can achieve sustained viral response (SVR), resulting in the cessation of fibrosis progression in the majority of patients, and minimizing the risk of HCC.

The current standard antiviral therapy for HCV infection in China is peginterferon and ribavirin. We have tried to optimize treatment for hepatitis C. The 11th Five-Year Plan-'National S&T Major Project for Infectious Diseases Control' (2008ZX10002-013) research is mainly concerning the clinical outcome of chronic hepatitis C, the mechanism and the optimizing treatment for difficult-to-treat patient with chronic hepatitis C virus infection. These projects are subgrouped in four main programmes: (1) Establish a large long-term follow-up cohort of chronic HCV infection in more than 2000 patients (2) Establish three optimizing treatment protocols and the individualized treatment strategy for difficult-to-treat hepatitis C. (3) Identify the mechanism of difficult-to-treat hepatitis C (4) Research and development of the novel therapy for difficult-to-treat hepatitis C. Finally, we have got very good antiviral efficacy for these difficult-to-treat patient with HCV. The SVR rates were 78.7%, 75.9%, and 58.0% in treatment naïve patients, recurrent patients and non-responders respectively.

- 5 We have also sponsored National HCC screening program.

Although we have got some achievement in prevention and care of HCV related HCC, we still face a lot of challenges.

- 1 Public awareness of hepatitis C is relative low in China. It is estimated that <3% of those infected had been diagnosed and as of 2012, only half of those diagnosed had been treated. One survey of 1362 physicians (nonspecialists for hepatitis C) in over 200 cities in 30 provinces showed physicians had very limited understanding of hepatitis C such as diagnosis, treatment, and prevention.
- 2 Because of the aging of populations and delays in diagnosis of hepatitis C because of low public awareness of the disease, many Chinese patients seen in clinics are presented with advanced liver disease. The proportion of patients with cirrhosis has increased in recent years. A recent observation about patients who have cirrhosis within the Beijing Medical Insurance System showed that those with cirrhosis secondary to hepatitis C have increased from 6.34% in 2004 to 9.33% in 2009.
- 3 No DAA are licensed in China. We have done Phase III clinical trial for simeprevir, daclatasvir and asunaprevir. And we will do Phase III clinical trial for sofosbuvir, ABT450/r/ABT267/ABT333 and MK-5172/MK-8742. But it will take several years for these drugs to be on the market in China. And we need to take into account the high price of DAA drugs.
- 4 HCC can occur in the patients after antiviral therapy, even the patients have got SVR.

In summary, our direction for controlling HCV related HCC in future is early diagnosis of hepatitis C infection and more effective treatment.

Speaker's Curriculum Vitae

Name Masao Omata
Position President
Institution Yamanashi Central and Kita
Hospitals
Honorary Professor, University of
Tokyo



Prof. Masao Omata graduated from Chiba University School of Medicine (Dr. Okuda), and continued his training at Yale University (Dr. G Klaskin) and in the Liver Unit at University of Southern California (Dr. RL Peters). After 6 years in US, he returned to the Department of Medicine at Chiba University in 1989, and started molecular biological study on Hepatitis B virus.

In 1992, he became Chairman of Second Department of International Medicine at University of Tokyo, and then subsequently became chairman of Department of Gastroenterology. Under his leadership, the Department of Gastroenterology had become one of the foremost centers in its field.

He is the president of the two (Yamanashi Central and Kita) hospitals at Kofu city, west of Tokyo, where, although scenic place with Mt. Fuji, hepatitis virus infection is epidemic and his homeland.

He has made an effort to revitalize the APASL (Asian Pacific Association for the Study of the Liver) with Dr. S. Sarin and others for the last 10 years. He is Co-Editor in Chief of the Hepatology International, an official journal of APASL.

As of October 1, 2014, he and his colleague have published 1,111 articles in English Literature including, 58 Hepatology, 43 Gastroenterology, 6 Ann Int Med, 6 Lancet, 5NEJM. Total impact factor 5,943/Citations 36,021 times/H-index 97.

S1-5**Summary and Special Comment by Chair***Masao Omata*

Session 2

Molecular Classification, Pathogenesis and Biomarkers

Speaker's Curriculum Vitae

Name Peter Schirmacher
Position Director
Institution Institute of Pathology, University
Hospital Heidelberg, Heidelberg,
Germany



Peter Schirmacher is the Director of the Institute of Pathology of Heidelberg University since 2004, coordinator of the SFB/TRR77 'Liver Cancer', funded by the German Research Foundation, and principal investigator of the German 'Virtual Liver' Network and several German consortial Health Research Networks (DKTK, DZL, DZIF). He is also founder and coordinator of the Tissue Bank of the National Center for Tumour Diseases (NCT), the comprehensive BioMaterialBank Heidelberg (BMBH) and the central Biobanking structures of DKTK and DZIF and has long-term experience in translational clinical studies. He is co-founder of the Liver Cancer Center Heidelberg (LCCH). Peter Schirmacher studied Medicine at Mainz University (graduation 1987, MD degree 1987) and Molecular Biology at Albert Einstein College, New York.

Professor Schirmacher is Chairman of the German Society of Pathology (since 2012) and Board member of the International Liver Cancer Association (ILCA) (since 2013), the German Telematic Platform (TMF) (since 2014) and the German Liver Foundation.

His research interests center on Molecular Tumor Pathology, especially of the liver, the Pathology of chronic liver diseases, the translation of these research findings into molecular diagnostics and associated technologies such as biobanking and virtual microscopy. He has published over 480 research papers and has participated in numerous diagnostic and therapeutic trials, preclinical research studies and clinical guidelines.

S2-1

Integrated Morpho-Molecular Classification of Hepatocellular Carcinoma

Peter Schirmacher

Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Integrated morpho-molecular classification is the aim and basis of the current WHO-classification of tumors. This has not been implemented for HCC in part due to the lack of sufficient correlative molecular data and respective integrative analyses. There have been extensive whole exomic sequencing efforts; despite unraveling some molecular alterations and defining molecular classes based on stochastic analyses of mainly genomic alterations, it has fallen short of identifying distinct HCC subentities of prognostic and even predictive potential. Thus, further progress necessitates the implementation of the new concept of integrated assessment of morphological and molecular pattern in combination with the comprehensive assessment of rare HCC subentities.

As many other cancer entities HCC includes a significant number of rare subentities that provide peculiar diagnostic and clinical pattern, but are constantly missed in all large scale molecular profiling efforts: Fibrolamellar HCC has long been known for its specific morphological features and has recently been shown to be based on the diagnostic DNAJB-PRKACA-translocation (Honeyman et al., 2014; Graham et al., 2015)). The recently described chromophobe HCC exhibits the alternative lengthening of telomeres (ALT) mechanism as unifying molecular characteristic (Wood et al., 2013). Extensive morpho-molecular classification of liver cell adenomas has identified a specific subentity characterized by β -Catenin Exon 3 mutations (leading to nuclear β -Catenin expression and GS overexpression) that may exhibit borderline features of malignant transformation to HCC (Pilati et al., 2014). Further peculiar morphological HCC subentities await comprehensive molecular classification. Considering the group of 'standard' HCCs, reciprocal molecular-morphological validation may further help to identify relevant pattern.

In conclusion, meticulous morphological subclassification provides the basis for identifying distinct, sometimes rare molecular entities, that are otherwise missed and carry highest exploratory potential. In turn, molecular profiling may pave the way for the identification of peculiar morphological pattern or differential diagnostic markers that improve diagnostic classification of HCC. Comprehensive morpho-molecular classification of HCC will improve diagnostic and clinical management, trial design and stratification, as well as basic and bedside-bench research in HCC.

Speaker's Curriculum Vitae

Name Augusto Villanueva, MD, PhD
Position Assistant Professor of Medicine
Institution Liver Cancer Research Program
(Tisch Cancer Institute), Icahn
School of Medicine at Mount Sinai,
USA



Dr. Villanueva received his medical degree in 1999 from the University of Santiago de Compostela (Spain), being awarded with the National Prize of Medicine. In 2004 he became board certified in Gastroenterology and Hepatology and between 2005–2008 he worked as a post-doctoral fellow in the Division of Liver Diseases at Mount Sinai (New York). Then, he moved to the HCC Translational Research Laboratory (BCLC, Hospital Clinic, Barcelona) and act as the Scientific Manager of the Heptromic Consortium until 2013. Later, he joined the Institute of Liver Studies at King's College (London) as Senior Lecturer. Since 2014, he is a faculty member of the Liver Cancer Program at Mount Sinai (New York), focusing on different molecular aspects of hepatocellular carcinoma, including minimally invasive biomarkers and resistance to systemic therapies. He has published original articles in top journals in the field such as *N Engl J Med*, *Nat Genet*, *Gastroenterology*, *Hepatology*, *J Hepatol*, among others. He is also associate editor for the *Journal of Hepatology* and *Liver Cancer*.

S2-2

Molecular-Based Stratification in HCC: Classification and Oncogene Addiction

Augusto Villanueva

Assistant Professor of Medicine, Liver Cancer Research Program (Tisch Cancer Institute), Icahn School of Medicine at Mount Sinai, USA

In hepatocellular carcinoma (HCC), current evidence in terms of mutational landscape identifies *TP53*, *CTNNB1* and *TERT* promoter mutations as the most frequently mutated genes. Interestingly, some of these changes are present in preneoplastic lesions, such as *TERT* mutations in dysplastic nodules, suggesting a potential role as tumor gatekeeper. At present, none of them are actionable targets nor can be used as predictive biomarkers. More rare mutations, affecting less than 5% of patients, are under evaluation as predictive biomarkers, such as response to a MEK inhibitor (refametinib) in patients with *RAS* mutations. In terms of DNA amplification, different studies have shown that around 10% of HCC patients have high-level amplifications of chromosome 11q13, locus of candidate oncogenes such as *CCND1*, *ORAOV1* or *FGF19*. Experimental evidence suggests that *FGF19* inhibition, one of the ligands of the FGF pathway, has anti-tumoral effects in HCC. Unfortunately, none of the trials testing *FGFR* inhibition with brivanib was able to show a significant improvement in patient survival.

Gene expression profiling enables classification of HCC in at least 2 major subclasses. One class is broadly characterized by an enrichment of signals related to cell proliferation and progression in the cell cycle (*Proliferation class*) and is generally associated with a more aggressive phenotype, while the second class lacks these strong proliferative signals and generally retains molecular features resembling normal hepatic physiology (*non-Proliferation class*). Some candidate oncogene addiction loops are enriched in these classes, mainly in the Proliferation class. Unfortunately, this knowledge hasn't translated yet into changes in patient's decision making. By the end of 2013, four drugs (i.e., sunitinib, erlotinib, linifanib and brivanib) have been unable to improve or parallel sorafenib's results in randomized controlled trials, despite some of them were reported to have some efficacy signals in phase 2. This includes trials testing drugs in first and second line, as well as in the adjuvant setting. Survival benefits provided by targeting oncogenic addiction loops are expected to add survival benefits to the backbone HCC therapy that currently relies on sorafenib. Its wide inhibitory profile, in addition to an anti-angiogenic effect and good safety profile confirms sorafenib as the benchmark for systemic management of HCC. The bottleneck of this approach will be drug toxicity. The trade-off between efficacy and side effects is pivotal in this scenario, since cirrhotic patients are clearly more susceptible to drug adverse events.

Speaker's Curriculum Vitae

Name Kazuto Nishio, MD, PhD
Position Professor and Chairman
Institution Department of Genome Biology,
Kinki University Faculty of
Medicine, Kyoto, Japan



Professional History:

1986	Graduate of Wakayama Medical University, M.D. Degree
1988–1990	Medical Staff, Fourth Department of Internal Medicine, Wakayama Medical University Hospital
1990–1992	Research Resident, Foundation for Promotion of Cancer Research at National Cancer Center Research Institute
1992–1996	Research Staff, Pharmacology Division, National Cancer Center Research Institute
1994	Ph.D. Degree, Wakayama Medical University
1996–2006	Head, Section of Drug Resistance, National Cancer Center Research Institute
2000–2006	Director, Translational Research Laboratory, National Cancer Center Hospital
2003-present	Invited Professor, Department of Internal Medicine, Kitasato University School of Medicine
2005-present	Expert Member, Pharmaceuticals and Medical Devices Agency
2006-present	Professor and Chairman, Department of Genome Biology, Kinki University School of Medicine
2006–2007	Invited Researcher, Genetics Division, National Cancer Center Research Institute
2010-present	Invited Professor, Kyoto Prefectural Medical University

Research Interests:

Translational Research (Molecular Correlative Study), Anticancer Drugs, Signal Transduction, Drug Resistance, Molecular Targeted Agents.

Membership of Academic Societies:

Japanese Cancer Association (Councilor), Japanese Society of Medical Oncology (Director), Japanese Association for Molecular Target Therapy of Cancer (Director), Japan Society of Clinical Oncology (Councilor), Japanese Society of Chemotherapy (Councilor), Japan Lung Cancer Society (Scientific Committee Member), American Association for Cancer Research, American Society of Clinical Oncology, International Association for the Study of Lung Cancer and others.

S2-3

Targeted DNA and RNA Sequencing of Fine-Needle Biopsy FFPE Specimens in Patients with Unresectable Hepatocellular Carcinoma Treated with Sorafenib

Kazuto Nishio¹, Kazuko Sakai¹, Haruhiko Takeda^{2,7}, Norihiro Nishijima², Etsuro Orito³, Kouji Joko⁴, Yasushi Uchida⁵, Namiki Izumi⁶

¹Department of Genome Biology, Kinki University School of Medicine, Japan, ²Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan, ³Department of Gastroenterology and Hepatology Nagoya Daini Red Cross Hospital, Japan, ⁴Center for Liver-Biliary-Pancreatic Diseases, Matsuyama Red Cross Hospital, Japan, ⁵Department of Gastroenterology, Matsue Red Cross Hospital, Japan, ⁶Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Japan, ⁷Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto, Japan

The multi-kinase inhibitor sorafenib is now used as standard therapy for advanced hepatocellular carcinoma. Predictive biomarkers of response to sorafenib are thus necessary. The purpose of this study was to assess the feasibility of using targeted DNA and RNA sequencing to elucidate candidate biomarkers of sorafenib response using fine-needle biopsy, formalin-fixed paraffin-embedded specimens in patients with hepatocellular carcinoma. Targeted DNA and RNA deep sequencing were feasible for the evaluation of fine-needle biopsy FFPE specimens obtained from 46 patients with HCC treated with sorafenib. Frequent mutations of suppressor genes, such as *CTNNB1* (34.8%) and *TP53* (26.1%), were detected in the HCC tumors. After excluding these suppressor genes, the average numbers of detected oncogene mutations differed significantly between the non-PD and PD groups ($P = 0.0446$). This result suggests that the oncogene mutational burden in the tumor might be associated with the clinical response to sorafenib. We have identified candidate gene expression (*NRG1*) in tumor for the prediction of sorafenib response (PFS) by RNA sequencing. Our findings provide new insights for tumor heterogeneity and allow us to discuss future therapeutic strategies.

Speaker's Curriculum Vitae

Name Lewis R. Roberts, MB ChB, PhD, FACP
Position and Institution Peter and Frances Georgeson
Professor in Gastroenterology
Cancer Research
Director, Hepatobiliary Neoplasia
Clinic
President, Africa Partners Medical
Division of Gastroenterology and
Hepatology, Department of Medicine,
Mayo Clinic, Rochester, MN, USA



Dr. Roberts was born in Kumasi, Ghana and earned his medical degree from the University of Ghana Medical School in Accra, Ghana. He then moved to the United States where he earned a Ph.D. degree in Physiology and Biophysics from the University of Iowa. Subsequently, Dr. Roberts completed residency training in Internal Medicine and a Clinician-Investigator Fellowship in Gastroenterology and Hepatology at Mayo Clinic, followed by training in Cancer Genetics as a Mayo Foundation Scholar.

Dr. Roberts's clinical and research interests focus on prevention, diagnosis and treatment of liver and biliary cancers. He has a strong interest in improving care for individuals with hepatitis and liver cancer in Africa as well as in immigrant African communities in the United States. Dr. Roberts's research has been funded by the National Institutes of Health, The Robert Wood Johnson Foundation, the AGA Research Foundation, and The Cholangiocarcinoma Foundation. He has authored over 200 articles, book chapters, editorials, review articles and commentaries and over 250 scientific abstracts. He currently serves on the Steering Committee of the Hepatocellular Carcinoma Epidemiology Consortium (HCCEC), as the coordinator of the International Hepatobiliary Neoplasia Registry and Biorepository (IHNB), as a member of the National Cancer Institute Hepatobiliary Cancers Task Force and as External Co-Chair of The Cancer Genome Atlas (TCGA) Hepatocellular Carcinoma and Cholangiocarcinoma Projects. He is a member of the editorial boards of *Hepatology*, *Liver Cancer*, and *Hepatic Oncology*.

Dr. Roberts has a strong interest in strengthening the capabilities of health care workers throughout Africa. He currently serves as President of Africa Partners Medical, a non-profit organization focused on reducing needless illness and death in Africa.

S2-4

Novel Insights from the Cancer Genome Atlas Hepatocellular Carcinoma Project

Lewis R. Roberts, David A. Wheeler, the TCGA Liver Cancer Analysis Working Group

Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN, USA

Background: Hepatocellular carcinomas (HCCs) are heterogeneous primary liver cancers with pleomorphic histologic features. We present a comprehensive genetic, genomic, transcriptomic and proteomic analysis of 192 HCCs in The Cancer Genome Atlas Program (TCGA) on behalf of the TCGA Liver analysis working group to provide a deeper understanding of the molecular features of HCCs, to classify them in a clinically-relevant manner, and to provide a public resource that identifies potential targets for emerging therapies.

Results: Mutation analyses confirmed the presence of TERT promoter mutations in 40% of HCCs. The analysis also revealed the first reported germline mutation in the TERT promoter in a 30 year old male, possibly reflecting an inherited predisposition to HCC. TERT promoter mutations were enriched in hepatitis C virus infected subjects. Analyses of hepatitis B virus (HBV)-induced HCCs demonstrated recurrent integrations of HBV in the TERT locus. Thus, HBV integration may substitute for TERT promoter mutations as an alternate mechanism of telomerase activation.

Other tumor suppressor genes inactivated by mutation included the cell cycle genes TP53 (32% of cases), RB1 (8%), and PTEN (3%), the Wnt/beta catenin pathway gene AXIN1 (4%), and the chromatin remodeling genes ARID1A (9%), BAP1 (6%), ARID1B (4%), ARID2 (4%), and PBRM1 (3%). The oncogene CTNNB1 was mutated in 27% of HCCs. Mutations were also found in the MTOR pathway genes, MTOR (4%), TSC2 (4%) and TSC1 (3%). The patterns of mutational signatures observed included signatures characteristic of the known carcinogens aristolochic acid and aflatoxin B1.

Clustering of mRNA, miRNA, or protein expression, DNA hypermethylation and DNA copy number profiles identified five, four, two, five and three clusters, respectively. Analysis of mRNA expression data identified five groups. In particular, Group 1 was associated with Asian race, higher histologic grade, and micro- and macrovascular invasion. Integrated clustering showed a grouping of HCCs into three superclusters: iCluster 1 had a low frequency of CDKN2A silencing, lack of CTNNB1 mutation, a normal-like methylation pattern, and overexpression of proliferation marker genes; iClusters 2 and 3 had a high frequency of CDKN2A silencing, CTNNB1 mutation, and overexpression of oxidative response genes; iCluster 3 tumors had a higher degree of chromosomal instability, high frequency of 17p loss, and a highly altered methylation profile.

Copy number aberrations included gains in the MYC, VEGFA, CCND1, TERT, and MET loci and losses in the TP53, RB1, ERFFI1, CDKN2A, ARID1A and PTEN loci.

Conclusion: Based on integrated analysis of genome, transcriptome, methylome and proteome we showed that HCCs naturally separate into three distinct groups with associated molecular and clinical characteristics. Importantly, we identified a novel germline mutation in the TERT promoter that may be associated with an inherited risk for HCC.

Speaker's Curriculum Vitae

Name Irene Oi-Lin Ng
Position Chair Professor and Head
Loke Yew Professor in Pathology,
and Director of State
Key Laboratory for Liver Research
Institution Department of Pathology,
Li Ka Shing Faculty of Medicine,
The University of Hong Kong



Irene Ng graduated with an M.B.B.S. degree from the University of Hong Kong in 1980. After her medical internship, she joined the Department of Pathology at the University of Hong Kong, where she obtained her MD and PhD degrees in molecular pathology in 1994 and 2005, respectively. Professor Ng currently is Loke Yew Professor in Pathology, Chair Professor, and Head of Department of Pathology at The University of Hong Kong. She is also the Director of the State Key Laboratory for Liver Research.

Professor Ng has published more than 340 peer-reviewed journal articles. She is among the top 1% of most cited scientists in 'Clinical Medicine' and 'All Fields' of ISI Essential Science Indicators. She is the Director of the State Key Laboratory for Liver Research. She is a member of the Grant Review Board of the Research Council of the Food and Health Bureau of Hong Kong and has served as on the Hong Kong Research Grants Council (Panel of Biology and Medicine). Currently, she is a member of the editorial board of Liver Cancer and was previously an associate editor of Liver International, academic editor of PLoS ONE, and editorial board member of Hepatology.

Her research work focuses on the molecular pathogenesis and pathology of liver cancer, including liver cancer stem cells and identification and characterization of important genes and signaling pathways. She has established useful pathological and biological parameters with prognostic significance for patient management. Her research studies have provided insight in the understanding of liver cancer development and may help to identify potential targets in novel cancer therapy.

Research Interests: Hepatopathology, HCC, molecular pathology and pathogenesis.

S2-5

Hepatocellular Carcinoma – Molecular Pathogenesis, Cell Signaling, and Cancer Stem Cells

Irene O.L. Ng

Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Hepatocarcinogenesis is a multistep process evolving from chronic hepatitis and cirrhosis to hepatocellular carcinoma (HCC). Recent advances in molecular methods have led to a growing understanding of the underlying mechanisms of hepatocarcinogenesis. Deregulation in many cell signaling pathways is implicated in tumor proliferation, progression, and survival. Several signaling cascades have been consistently found to be dysregulated in HCC. This presentation attempts to highlight some of the signaling pathways we have been working on and implicated in the pathogenesis of HCC. More recent evidence also suggests the involvement of liver-specific cancer stem cells in hepatocarcinogenesis. In addition, cancer stem cells or tumor-initiating cells (T-ICs) are a subpopulation capable of self-renewal and tumor initiation, and are more resistant to chemotherapeutic drugs. Using in vitro and in vivo models, we have identified CD24 and CD47 as novel liver cancer stem cell markers. I will also present some of our recent translational work based on genomic analysis of HCC. This presentation attempts to highlight the molecular mechanisms and signaling pathways currently implicated in the pathogenesis of hepatocellular carcinoma. Detailed understanding of the molecular pathogenesis is crucial for the development of new therapeutic approaches against hepatocellular carcinoma.

Session 3

New Insights in Imaging

Speaker's Curriculum Vitae

Name Byung Ihn Choi
Position Clinical Chair Professor
Institution Department of Radiology,
Chung-Ang University Hospital



Dr. Choi is a clinical chair professor of radiology at Chung-Ang University medical center. He is a Past chair of the Department of Radiology at the Seoul National University Hospital, and is also a former president of 5 national and international societies including The Korean Society of Radiology (KSR), Asian Oceanian Society of Radiology (AOSR), the Asian Society of Abdominal Radiology (ASAR) and Asian Federation of Societies of Ultrasound in Medicine and Biology (AFSUMB), and member of executive committee of 7 International organizations of Radiology including International Society of Radiology (ISR). He is an honorary member of 10 international and regional societies including RSNA and ESR. He is also an honorary fellow of 3 prestigious college of radiology including American College of Radiology (ACR). Dr. Choi is a world renowned abdominal radiologist, particularly in the field of hepatobiliary imaging. He is a tireless and prolific clinical and scientific researcher, devoted teacher, and an outstanding clinician. Dr. Choi has authored more than 430 scientific papers and 30 textbooks, and presented more than 370 lectures internationally.

Research Interest:

1. Evaluation of abdominal imaging techniques inducing Ultrasound, CT, MRI and fusion imaging.
2. Development of new abdominal radiology procedures.
3. Development for early detection of abdominal cancer including liver, biliary tree, pancreas and gastrointestinal tract.
4. Evaluation of quantitative diagnosis of abdominal cancer by functional imaging technologies.
5. Mentoring fellows and residents in abdominal radiology research.

S3-1

HCC and Mimickers: Imaging Diagnosis

Byung Ihn Choi

Department of Radiology, Chung-Ang University Hospital, Seoul, Korea

Key imaging features for the diagnosis of HCC are contrast enhancement during the hepatic arterial phase and washout during the portal venous and equilibrium phase images, capsular rim enhancement on portal venous and delayed phase images, moderate hyperintensity on T2-W1, conrona enhancement, hypointensity on hepatobiliary phase after administration of hepatobiliary contrast agent, and restricted diffusion on DWI.

Among the imaging characteristics of HCC, arterial enhancement is considered the most consistent feature of HCC. However, other arterially enhancing nonmalignant lesions can also be seen in the cirrhotic liver, especially those measuring smaller than 2 cm in diameter, which mimic HCC. Those arterially enhancing pseudolesions are transient arterial enhancement due to non-tumorous arterioportal (AP) shunts or focal obstruction of a distal parenchymal portal vein, and are typically seen as well-defined areas of enhancement only on the arterial phase and not on other phase. In addition, most HCCs show hypointensity on hepatobiliary phase imaging and a hyperintensity on high b-value DWI, whereas early enhancing pseudolesions show isointensity on both hepatobiliary phase images and DWI.

Fibrosis is frequently found cirrhotic liver and usually in a lattice-like network throughout the liver. Focal confluent hepatic fibrosis observed in end-stage liver disease can be mass-like in appearance and therefore mimic HCC.

Other arterially enhancing hepatic tumor such as hemangioma, focal nodular hyperplasia (FNH), hepatic adenoma, and angiomyolipoma, can also mimic HCC.

Mass-forming intrahepatic cholangiocarcinoma is also occasionally misinterpreted as an HCC, particularly in case of small mass-forming intrahepatic cholangiocarcinoma, arterial enhancement can be seen. Intrahepatic biliary duct dilation distal to the tumor and associated capsular retraction are features more commonly associated with mass-forming intrahepatic cholangiocarcinoma and are rarely seen in association with HCC.

Hypervascular metastases can mimic HCC when they developed in cirrhotic liver. Hypervascular metastases frequently come from renal cell carcinoma, ovarian cancer, pancreatic neuroendocrine carcinoma, and medullary thyroid cancer.

Speaker's Curriculum Vitae

Name Jeong Min Lee, MD, PhD
Position Professor
Institution Department of Radiology
Seoul National University Hospital



Jeong Min Lee studied Medicine at Chonbuk National University and graduated in 1990. Following this, he completed a clinical fellowship in the same Hospital. Professor Kudo is currently a Professor and the chief radiologist at abdominal imaging section of the Department of Radiology, Seoul National University Hospital since 2008.

Professor Lee has published 270 International scientific peer review papers in well-regarded journals. He has given more than 50 invited lectures in the area of his expertise on numerous occasions to international audiences. He serves as an Executive Council Board Member for Korean Society of Radiology, Korean Abdominal Society of Radiology and Korean Society of Magnetic Resonance Imaging and Medicine. Professor Lee is also serving as an Associate Editor of LIVER CANCER (Karger), and editorial board member of Korean Journal of Radiology.

His research interest is 'Diagnosis and noninvasive treatment of HCC'. Professor Lee participated into preparation of HCC guidelines Proposed by APASL, KLCSSG-NCC and LI-RADS by ACR.

Research Interest: Hepatology, Diagnosis and RF ablation of HCC.

S3-2

Differentiation of Intrahepatic Mass-Forming CCC from HCC on EOB-MRI

Jeong Min Lee

Department of Radiology, Seoul National University Hospital, Seoul, Korea

Gadoxetic acid (Gd-EOB-DTPA)-enhanced liver MRI has been increasingly used for the diagnosis and staging of liver malignancies including hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC), as hepatobiliary phase (HBP) images have been shown to provide additional valuable information for the detection of small malignant tumors as well as for characterization of cirrhotic nodules. The differential diagnosis of IMCC and HCC is usually based on well-known imaging features of IMCC, such as a hypovascular tumor with a lobulated contour, accompanying adjacent intrahepatic duct (IHD) dilatation, and liver capsule retraction. Characteristic enhancement patterns of IMCC using conventional extracellular contrast media (ECCM) include peripheral rim enhancement or weak enhancement at the arterial phase (AP) followed by gradual centripetal or persistent enhancement on the portal venous phase (PVP) and delayed phase at computed tomography (CT) or magnetic resonance imaging (MRI). However, its discrimination from HCC, especially for small tumors, remains challenging in clinical practice owing to IMCC's often atypical enhancement pattern. Furthermore, the uptake of gadoxetic acid by hepatocytes resulting in the enhancement of underlying liver parenchyma begins around or right after the PVP, the relative hyperenhancement of the background liver parenchyma during the transitional phase (TP) can obscure the true temporal enhancing pattern of IMCCs leading radiologists to misinterpret the tumor signal intensity (SI) as being hypointense or showing 'pseudo wash-out'. Therefore, knowledge of the morphologic feature, enhancement characteristics and HBP of IMCC and HCC on gadoxetic acid-enhanced MR imaging could improve their accurate diagnosis, resulting in better therapeutic planning. In this lecture, I would like to address the differential imaging features of IMCC from HCC on gadoxetic acid-enhanced MRI including diffusion weighted imaging and HBP imaging.

Speaker's Curriculum Vitae

Name Osamu Matsui
Position Professor
Institution Department of Advanced Medical
Imaging, Kanazawa University
Graduate School of Medical
Sciences, Japan



Dr. Osamu Matsui is a graduate of Kanazawa University Faculty of Medicine in 1972 and completed radiology residency at Kanazawa University hospital. In 1982, he became a visiting fellow for the Department of Radiology at the University of Cincinnati in the United States and at the University of Lund in Sweden. Dr. Matsui was promoted to full professor and chairman for the Department of Radiology, Kanazawa University in 1999. In 2010, he was appointed for the dean of Kanazawa University Graduate School of Medical Science, and is now the specially appointed research professor of the Department of Advanced Medical Imaging and professor of emeritus at the same institute. His main clinical and research contributions have been in the diagnostic imaging and interventional radiology, especially for liver cancer. He is the author of around 400 original English papers which appeared in Medline. He was the editor-in-chief of Japanese Journal of Radiology which is the official journal of Japan Radiological Society, and now an associate editor of gastrointestinal section of Radiology. He was selected one of the distinguished scientists of Japan in 2009 by the Minister of Education, Culture, Sports, Science and Technology.

S3-3

Gd-EOB-DTPA Enhanced MRI as an Imaging Biomarker for Activation of β -Catenin Signaling in Hepatocellular Tumor/Hyperplasia

Osamu Matsui

Department of Advanced Medical Imaging, Kanazawa University
Graduate School of Medical Sciences, Kanazawa, Japan

Gd-EOB-DTPA) is taken up by hepatocytes and then excreted into bile ducts by membrane transporters. Two separate analyses noted highly significant positive correlations between the uptake transporter OATP1B3 expression level and enhancement ratio on hepatobiliary phase (HB) phase in HCC, indicating that the signal intensity on HB phase of EOB-MRI was a sensitive (indirect) molecular imaging reflecting expression of OATP1B3 in HCC.

Majority of hypervascular classic HCCs showing hyperintensity on HB phase (hyperintense HCC) were moderately differentiated HCC but less aggressive biologically with significantly lower recurrence rate and better survival than hypointense HCC. Majority of hyperintense HCCs showed significantly increased expression of HepPar-1 (hepatocyte marker), intra-nuclear β -catenin and glutamine synthetase (GS) on immunohistochemical staining, consistent with 'HCC with β -catenin mutation'. Genetic analysis revealed that HCC with OATP1B3 high expression HCC was a genetic subtype with up-regulation of mature hepatocyte function related markers and down-regulation of hepatic stem/progenitor related markers. Transcription factor analysis identified hepatocyte nuclear factor 4A (HNF4A) as the most intensively activated factor in OATP1B3-high HCC, and experimental study with HNF4A knock-down HCC cells from a hyperintense HCC revealed that OATP1B3 expression was intensively regulated by HNF4A was considered to be a key factor for regulating GS and OATP expression in zone 3 of hepatocytes in collaboration with Wnt/ β -catenin pathway.

Majority of hepatocellular adenoma (HCA) showed hypointensity on HB phase, but HCA with β -catenin mutation which has a potential of malignant transformation commonly demonstrated hyperintensity with OATP1B3 and GS overexpression. Majority of focal nodular hyperplasias (FNH) showed hyperintensity on HB phase, and OATP1B3 overexpression was exclusively observed in almost the same areas with map-like GS expression. Recent transcriptome analysis of FNH identified an activation of Wnt/ β -catenin pathway, although without any mutations in the β -catenin gene. Similar correlation between hyperintensity on HB phase and OATP1B3 and GS overexpression was seen in nodular regenerative hyperplasia and peritumoral hyperplasia.

These indicated that hyperintensity on HB phase can be an imaging biomarker for β -catenin mutation/activation in hepatocellular tumor/hyperplasia. Function of HNF4A in over-expressing OATP1B3 in these lesions should be further investigated.

Speaker's Curriculum Vitae

Name Takamichi Murakami
Position Professor and Chairman of Radiology
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Professor Murakami graduated from Kobe University School of Medicine in 1986, and then completed postgraduate training at the Osaka University Graduate School of Medicine in 1991. From 1991–2006, he then became Fellow, Assistant Professor, and Associate Professor of Radiology at the Osaka University Graduate School of Medicine. Professor Murakami was Visiting Assistant Professor of Radiology, University of Pittsburgh Medical Center (1994–1995). He is currently Professor and Chairman of Radiology at the Kinki University Faculty of Medicine; a position he has held since 2006.

Professor Murakami was a member of the Task Force on Computed Tomography for the 1999 International Commission on Radiological Protection, and he has also received a number of awards including The Certificate of Merit Award: Radiological Society of North America (1991 [two], 1996 [two], 2006 [two], 2007 [one], 2008 [three], 2011 (one), 2013 (one)), Cum Laude Award: Radiological Society of North America (2009, 2013), Society of Computed Body Tomography and Magnetic Resonance (1996), and Misono Award: Association of Japan Radiological Effect and Protection (2004).

Professor Murakami has published more than 530 articles, and is on the Review Board of 14 peer-review journals. He has given more than 250 presentations in the area of his expertise on numerous occasions to international audiences. He is a member of the reviewer board of American Journal of Roentgenology, Investigative Radiology, Journal of Magnetic Resonance Imaging and European Radiology, etc. He is also a executive committee member of Japanese Radiological Society, Japanese Society of Magnetic Resonance in Medicine, Japanese Society of Interventional Radiology, and Asian Society of Abdominal Radiology, and Asian Society of Abdominal Radiology, a council member of Japanese Society of Hepatology and Japanese Society of Liver cancer Study Group, and a member of Radiological Society of North America and Society of Gastrointestinal Radiologists, etc.

Professor Murakami research interest is 'Radiological diagnosis and Interventional Radiology of abdominal disease'. Professor Murakami is studying dynamic MDCT and MR study for detection and diagnosis of liver tumor, especially hepatocellular carcinoma, and is also interested in a study about evaluation of segmental liver function by using perfusion CT and liver tissue specific MR contrast medium. About a field of Interventionl Radiology, Professor Murakami is interested in a study to improve efficacy of focal treatment of HCC, for example, US image navigation system for radiofrequency ablation and transcatheter arterial chemoembolization.

S3-4

New CT Technology for the Liver Imaging

Takamichi Murakami

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Dynamic study is essential for diagnosis of liver disease. Recent progress of MDCT can improve the detection, characterization and staging of liver tumor, and also enable us to perform 4D imaging, to obtain liver functional imaging, to evaluate contained material of the liver quantitatively. After contrast injection, multiphase helical CT images in the 160 mm scan range can be obtained during the 30 sec of breathhold with a newly developed scan cradle that can rapidly move back-and-forth continuously (Shuttle helical CT imaging). MIP/VR images reconstructed from each phase data can reveal not only morphologic information of vessel and tumor but also hemodynamics as 4D-CT angiography. By perfusion CT study, the hepatic perfusion parameters, such as tissue blood flow (TBF), tissue blood volume (TBV), mean transit time (MTT), and hepatic arterial fraction (HAF), can be calculated on a workstation using commercially available software package based on deconvolution algorithm. Perfusion CT study may reveal regional liver function.

Dual energy CT has the ability to make not only material density images but also monochromatic images with improving image quality against standard dual energy imaging. Optimal KeV monochromatic CT image can improve liver to tumor contrast of hypervascular HCC at arterial phase CT image. However, iterative reconstruction technique is required to reduce noise on low KeV monochromatic CT. From material density images such as water and iodine density images, we can have virtual non contrast images and iodine map and iodine phase color images that can reveal sequential distribution of iodine. Iodine map may evaluate liver fibrosis quantitatively. Multiple material decomposition (MMD) technique can calculate more than 2 material density images, and can measure percentage of contained material quantitatively. Now, MMD technique can estimate amount of fat deposition quantitatively.

Cone-beam CT using a flat-panel detector is very useful for transcatheter arterial chemoembolization (TACE) for HCC. It can provide good 3D angiography and cross-sectional, soft tissue imaging, and permits assessment of the complex vascular anatomy of the liver. In addition, recent developments in software programming have enabled automatic identification of the feeding vessels of the tumor on 3D angiography. It is very helpful for adequate treatment and precise evaluation of treatment effect.

I would like to introduce recent progress of CT technology for the liver imaging.

Speaker's Curriculum Vitae

Name Etsuro Hatano
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Pancreatic Surgery and
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Dr. Hatano graduated from Faculty of Medicine, Kyoto University in 1989. He entered Graduate School of Medicine, Kyoto University in 1994. During this period, he had been in charge of microscopic anastomosis of hepatic artery in pediatric living related liver transplantation. He had Ph Doctoral Degree in 1997. He continued the research concerning signal transduction in hepatocyte apoptosis in University of North Carolina at Chapel Hill under Professor David A Brenner from 1998 to 2000. He became Assistant Professor in Department of Gastroenterological Surgery, in 2002. In 2014, he became associate professor in Division of Hepatobiliary Pancreatic Surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Kyoto University. He was also Visiting Professor of Department of Digestive Surgery & Transplantation, University Hospital of Hautepierre, Strasbourg, France.

Dr. Hatano has been enthusiastic in extending the indication of hepatic surgery. To cure the patients with advanced hepatobiliary cancer, he has been making an effort to reduce the surgical stress by the laparoscopic surgery. Furthermore, he introduced pre- and post-operative adjuvant therapy for advanced cancer, resulting that conversion therapy to resection can be possible. He also served to clarify the role of salvage liver transplantation for HCC patients.

S3-5

Prediction of Microvascular Invasion in HCC

Etsuro Hatano, Tsung-Han Wu, Kenya Yamanaka, Satoru Seo, Kojiro Taura, Kentaro Yasuchika, Hideaki Okajima, Toshimi Kaido, Shinji Uemoto

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Microvascular invasion (mVI) is known to be the risk factor of recurrence in hepatocellular carcinoma (HCC) and affects treatment option. Several factors such as tumor size and tumor margin status on image, SUV and TNR from fluorine-18 fluorodeoxyglucose-positron emission tomography (18F-FDG-PET), and tumor markers have been proposed to predict mVI of HCC preoperatively. Among these factors, we had reported 18F-FDG-PET could predict tumor differentiation and prognosis preoperatively. The degree of HCC tumor differentiation had also been shown to correlate with the incidence of mVI. However, the values of these factors have not been fully validated. We hereby performed a retrospective analysis to validate the power of these preoperative factors to predict mVI in HCC patients.

Fifteen patients had mVI (mVI+ group) and 64 patients had no evidence of mVI (mVI-group) on pathological examination. Univariate analysis showed mVI+ group had higher SUV & TNR (5.2 vs. 3.8, $p = 0.02$ and 1.8 vs. 1.3, $p = 0.02$, respectively.) and higher portion of non-smooth tumor margin. (87% vs. 27%, $p = 0.0001$) Tumor markers showed no significant difference. Multivariate analysis showed only non-smooth tumor margin could predict mVI independently. (Odds Ratio: 18.3, 95% CI: 3.27–102.6, $p = 0.0009$)

Non-smooth tumor margin on pre-operative image, especially from EOB-MRI, predicts mVI of HCC. The prediction of mVI of HCC might be helpful to decision making of the following treatment.

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Session 4

New Aspects of Locoregional/Surgical Therapy

Speaker's Curriculum Vitae

Name Shi-Ming Lin, MD
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Department of Gastroenterology
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Memorial Hospital, LinKuo and
Taipei, Taiwan



Shi-Ming Lin studied medicine at National Taiwan University and graduated in 1982. Following this, he completed a clinical resident training in Veteran General Hospital Taipei and GI fellowship in Chang-Gung Memorial Hospital-Taipei and Linkuo. Dr. Lin is currently a Professor since 2007 and a deputy chairman at the Department of Gastroenterology and Hepatology, Chang Gung University since 2014.

Dr. Lin is one of the pioneers of RFA for liver tumors in Taiwan. Dr. Lin has published 106 papers in international and domestic scientific journals including Gastroenterology, Hepatology, Gut, Journal of Hepatology, Cancer, and British Journal of Surgery. Dr. Lin has 4 papers (published in Hepatology 1999 and Gastroenterology 2004, Gut 2005 and J Hepato 2007) ranked as the highly cited papers. Dr. Lin has given 110 invited lectures in the area of his expertise on occasions to international audiences including APASL (2006, 2008–9, 2012, 2013), APDW (2007, 09), Annual Microwave Surg Meeting Jpn (2008, 09), Kobe HCC symposium (2009), APPLE (2010–2014), 2013 Korea-Japan Image-guide Tumor Ablation Meeting, Japan JSH 2012, HK IDD 2011, HK Interventional Radiology Symposium 2009, South East Asian Nations conference (2008, 2010, 2012), and Singapore GI Annual Meeting 2009, Asian Congress of Tumor Ablation (ACTA) 2014, 4th International Kyoto Liver Cancer Symposium 2014, Mongolia DDW 2014, The Hepatic Oncology Multi-disciplinary Approach Symposium (TOMAS), Kuala Lumpur, Malaysia 2014, and Taiwan-France HCC symposium 2014. Dr. Lin is serving as a journal referee of many peer-review journals including Gastroenterology, Hepatology, Gut, J Hepatol, Ann Surg, et al.

His research interest include diagnosis and treatment of hepatoma and anti-viral therapies for hepatitis B and C.

S4-1

RFA with Multiple Electrodes for HCC >3 cm: Uni-Polar versus Bipolar Electrodes

Shi-Ming Lin

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Current RFA devices are effective for HCC <3 cm. Recently, application of a switching RF controller (SWC-RFA) with placement of 2–3 unipolar or bipolar RF electrodes has been reported to create a larger ablation in a shorter time. Very limited but promising preliminary results have been reported.

In our center, we enrolled 70 patients with at least one index HCC tumor >3.0 cm (between 1 January 2009 and 31 December 2011) treated with SWC-RFA with 2–3 RF electrodes. 53 (75.7%) patients had 58 index tumors of medium size (3.1–5 cm), and the remaining patients had 17 large tumors (5.1–7.0 cm). The mean diameters of the index tumors in medium size and large size groups were 3.7 ± 0.5 cm and 5.7 ± 0.6 cm, respectively. The rates of complete ablation after first session were 79.3% (46/58) and 82.4% (14/17), respectively. After an additional 1–2 RFA sessions, the rate of primary technique effectiveness (PTE) were 91.4% (medium-size tumors) and 94.1% (large tumors), respectively. After a mean follow-up of 21.0 ± 10.2 months, 12 (18.8%) patients exhibited local tumor progression (LTP) and 10 (14.3%) patients died. Estimated cumulative overall survival rates and LTP rates were 93.9% and 84.6% (1 year), 81.3% and 10.7% (2 years), and 17.2% and 32.8% (3 years), respectively. Comparing conventional RFA with single RF electrode and sequential ablation, the reported rate of complete ablation was 53–61% in medium-sized HCC and 20–45% in large HCC. Seror et al used SWC-RFA and showed 81% of complete ablation for HCC >5 cm and Lee et al showed 97% in HCC of 3.1–5 cm. Therefore, SWC-RFA with 2–3 electrodes achieved a high rate (>90%) of complete ablation for medium size and large HCC.

Moreover, SWC-RFA with multiple bipolar RF electrodes could create a larger coagulation necrosis by enabling placement of RFA electrodes with inter-electrode distances as great as 3 cm. This method may reduce the risk of tumor spreading in small HCC, since this technique permits the use of no-touch RFA for tumors <3 cm. We have analyzed our HCC patients undergoing SWC RFA between December 2008 and March 2014. For HCC <3 cm, comparing uni-polar (158 patients) with bipolar RFA (57 patients), the complete ablation after one session and PTE were 88.9% vs. 93.8%, PTE were 100% vs. 100% (P=NS); 3-year OS were 100% vs. 93.8% (p = 0.54); LTP at 2-years were 27.1% vs. 0% (non-touch method) (p = 0.054). For HCC of 3.1–5 cm and HCC >5 cm, no significant difference were encountered between both groups in terms of complete ablation, PTE, overall survival and LTP. Long-term follow up and larger sample size especially in SWC-RFA with bipolar electrodes would be required to elucidate the benefit of SWC-RFA with mono-polar and bi-polar electrodes.

Speaker's Curriculum Vitae

Name Riccardo Lencioni, MD, FSIR, EBIR
Position Professor and Director
Institution Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy



Riccardo Lencioni, MD, FSIR, EBIR, is board certified in Radiology and Gastroenterology. He is Professor and Director of Diagnostic Imaging and Intervention at Pisa University School of Medicine in Pisa, Italy.

Professor Lencioni is one of the world's foremost interventional oncology specialists, known especially for his highly influential work in liver cancer. He has been a leading member of several expert panels developing recommendations for research and clinical management of hepatocellular carcinoma. He has co-authored the white papers *Design and Endpoints in Clinical Trials in Hepatocellular Carcinoma* (2008), *Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma* (2010), and *EASL-EORTC Clinical Practice Guidelines: Management of Hepatocellular Carcinoma* (2012).

Riccardo Lencioni is the Chairman of the World Conference on Interventional Oncology. He is a co-Founder of the International Liver Cancer Association, in which he also acts as the Executive Secretary. He is an Associate Editor of the journal *Liver Cancer* and serves as an editorial board member or reviewer for several other titles.

Riccardo Lencioni has published 182 articles in peer-reviewed international journals indexed in PubMed and numerous chapters in textbooks of interventional radiology, gastroenterology, oncology and surgery. In addition, he has been the editor of nine books. According to the SCOPUS database, citations of his publications currently number in excess of 13,000 with an *h* index of 53. Riccardo Lencioni has been an invited or honorary lecturer at more than 450 international meetings or conferences.

S4-2

Management of Intermediate-Advanced HCC in the West

Riccardo Lencioni

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Despite the implementation of surveillance programs of at-risk populations, the majority of Western patients with HCC are diagnosed late, when curative treatments – including liver transplantation, hepatic resection, and image-guided ablation – cannot be applied. TACE is the most widely used treatment for HCC patients unsuitable for radical therapies. Randomized controlled trials and meta-analyses have shown that TACE improves survival with respect to best supportive care, extending the median survival from 16 to 19–20 months. As a result, TACE has been recommended as the standard of care for the treatment of unresectable, large or multinodular noninvasive tumors isolated to the liver, in patients with compensated cirrhosis. Distinct technical advances in the performance of TACE and improved patient selection and management took place since the completion of these studies. Several recent investigations have suggested that an optimized TACE protocol may offer substantially longer median survival. An open issue in the management of TACE-treated patients is the assessment of tumor response and the criteria for treatment discontinuation. It has been suggested that TACE should be discontinued in patients in whom an objective response in the treated tumor has not been achieved after two treatment cycles. While patients who present or develop extrahepatic spread are considered for systemic therapy with sorafenib, the management of those with locally-advanced disease is more controversial, especially given the data reported by multiple centers for radioembolization with Y90. Unfortunately, the clinical trials completed so far failed to provide evidence of unequivocal benefit associated with the concurrent use of loco-regional and systemic therapies. The next few years will yield important information as results from the on-going phase III trials further define the role of novel treatment options in HCC clinical management.

Speaker's Curriculum Vitae

Name Masatoshi Kudo, MD, PhD
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Masatoshi Kudo studied Medicine at Kyoto University and graduated in 1978. Following this, he completed a clinical fellowship in Kobe City General Hospital followed by a research fellowship at the University of California Davis Medical Center in USA and Kyoto University Graduate School of Medicine, where he received his PhD degree in Medical Science in 1987. Professor Kudo is currently a Professor and Chairman at the Department of Gastroenterology and Hepatology, Kinki University School of Medicine since 1999.

Professor Kudo has published 544 International scientific peer review papers in well-regarded journals in addition to 829 domestic scientific papers. He has given 314 invited lectures in the area of his expertise on numerous occasions to international audiences. He serves as an Executive Council Board Member for Liver Cancer Study Group of Japan (LCSGJ), Chairman of Nationwide Survey Committee of LCSGJ, and a representative of LCSGJ Head Office. Professor Kudo is also a President of the Japan Society of Ultrasonics in Medicine (JSUM), Immediate Past President of WFUMB, President-elect of AFSUMB, an Executive Board Member of Japan Society of Hepatology (JSH), a Founding Board member of International Liver Cancer Association (ILCA). He is also serving as an Editor-in-Chief of LIVER CANCER (Karger).

His research interest is 'Diagnosis and treatment of HCC'. Professor Kudo is the first author of 'Consensus-based Practice Guideline of HCC Proposed by Japan Society of Hepatology' published in 2007 and 2010, 2014 revised version.

S4-3

Management of Intermediate/Advanced HCC in Japan

Masatoshi Kudo

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I. Intermediate stage HCC

Treatment strategy of intermediate stage HCC in Japan is as follows;

1. Selective Lipiodol TACE for fewer/small HCC nodules.
 2. Drug eluting beads (DEB) TACE for intermediate size/number of HCC nodules.
 3. Hepatic arterial infusion chemotherapy (HAIC) for larger/multilobar multiple HCC nodules.
 4. Sorafenib for TACE/HAIC refractoriness
- According to nationwide data registered between 2001–2005, 5-year survival rate and MST of intermediate stage HCC were 30.0% and 38 months, respectively.

II. Advanced stage HCC

Treatment strategy of advanced stage HCC in Japan is as follow;

1. HAIC for HCC patients with major and minor vascular invasion (Vp1-Vp4).
 2. Superselective Lp-TACE for HCC patients with minor vascular invasion (Vp1-Vp2).
 3. Sorafenib for HCC patients with minor vascular invasion (Vp1-Vp3) and/or extra hepatic spread.
- According to nation wide data registered between 2001–2005, 5 year survival rate and MST of advanced HCC were 18.2% and 15 months, respectively.
- In conclusion, different from other countries HAIC and super selective Lip-TACE play a very important role in the relatively better outcome in intermediate/advanced HCC compared with those in other countries.

Speaker's Curriculum Vitae

Name Sheng-Long Ye, MD, PhD
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Sheng-Long Ye, MD, PhD is a Professor of Medicine and Oncology at Fudan University (formerly Shanghai Medical University), Shanghai, China. He received his medical education at Shanghai Medical University in Shanghai, China, where he was awarded his M.D., M.Sc. and Ph.D. He spent 4 years as a Visiting Research Scientist at the Harvard Medical School Deaconess Hospital in Boston, Massachusetts, U.S.A. before returning to China in 1992. He was Deputy Director of the Liver Cancer Institute and Chairman of the Department of Hepatic Oncology at Zhongshan Hospital, Fudan University, Shanghai, China. He was also Chief of the Key Laboratory of Carcinogenesis and Cancer Invasion for the Ministry of Education, China, which is also based at Fudan University.

Professor Ye specializes mainly in experimental and clinical study of liver cancer with emphasis on recurrence and metastasis, as well as biological and targeted therapy of cancer. He has published over 400 articles in Chinese or English. He holds membership for professional societies including Steering Committee Member of the Asia-Pacific Primary Liver Cancer Expert Association, Governing Board Member of the International Liver Cancer Association (2007–2011); Honorary President of the Chinese Society of Liver Cancer, and Executive Council member of the Chinese Anti-Cancer Association; Executive Council member of the Chinese Society of Hepatology, and Chairman of Chinese Liver Cancer Study Group; Executive Council member of the Chinese Society of Cancer Biotherapy, and other academic positions. He serves as an Associate Editor of the journal LIVER CANCER and member of the Editorial Boards for more than 20 journals.

S4-4

Current Management of HCC in China

Sheng-Long Ye

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Primary liver cancer (PLC) is a most common malignancy, and more than half of these cases are estimated to occur in China. PLC, of which hepatocellular carcinoma (HCC) accounts for about 90%, is the second cause of cancer deaths in China. The key problems for HCC treatment in Chinese patients are severe cirrhosis, portal vein invasion, distant metastasis, low resectability and high recurrence rate. The clinical guideline for management of HCC was approved by the Ministry of Health in China. The guideline for pathological diagnosis of liver cancer has recently been published in China. The clinical diagnosis of HCC is based on imaging examination and AFP. New biomarkers for clinical diagnosis and outcome prediction are investigated. The development of HCC is a long-term process of multistep malignant transformation. Early HCCs are frequently difficult to be differentiated from high grade dysplastic nodules (HGDNs). Primovist-enhanced MRI may provide a more valuable procedure for assessment and diagnosis of focal liver lesions.

TACE has become most commonly used modality for unresectable HCC in China. Recent data indicated that palliative resection for BCLC-B HCC might be considered to improve prognosis compared to TACE. Portal vein tumor thrombosis (PVTT) is one of the key problems of treatment efficacy and prognosis for HCC patients. Various procedures including surgery, TACE, radiotherapy, molecular targeted therapy and combination therapy are investigated to deal with PVTT in HCC patients.

The replication and activation of Hepatitis B/C viruses (HBV/HCV) are closely associated to the recurrence and progression of HCC. More attention has been paid to antiviral therapy on HBV/HCV-related HCC. An expert consensus of the indication and application of antiviral therapy in HBV/HCV-related HCC was published as a guideline for the treatment of HCC in China.

Novel interventional approaches to treating HCC have been developed in recent years. The local ablation is effective in HCC with solitary or ≤ 3 nodules of each ≤ 3 cm in diameter, no portal vein thrombosis, no distal metastasis, no hematological problem, and Child-Pugh A/B of liver function. Randomized clinical trials in China indicated similar survival and recurrence rates between surgery and RFA for small HCC. Combination of RFA with TACE is suitable for HCC of > 3 cm in diameter and Child-Pugh B cirrhosis.

Molecular targeted therapy revealed an encouraging outcome in inoperable and metastatic HCC patients. A nationwide large-scale clinical trial indicated that preventive administration of urea-based cream can decrease sorafenib-related hand-foot skin reaction in HCC patients. Intensive studies were applied to further investigate the efficacy of sorafenib combined with other treatment modalities, including surgical resection, ablation, TACE, chemotherapy and other molecular targeted therapies. Clinical trials with other new molecular targeted therapies in HCC patients were also conducted in China.

Speaker's Curriculum Vitae

Name Ken Shirabe, MD
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Education:

School of Medicine, Kyushu University, 1986

Professional Training and Employment:

1986–1987 Resident, Department of Surgery II, Kyushu University
1988–1990 Research Fellow, Department of Surgery II, Kyushu University
1990–1991 Resear Fellow, Department of Surgery, University of Minnesota
2001–2002 Assistant Professor, Department of Surgery and Science,
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2002–2004 Associate Professor, Department of Surgery and Science,
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2009–2012 Clinical Assistant Professor, Department of Surgery and
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2012.6-present Assistant Professor, Department of Surgery and Medical
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Japanese Society of Gastroenterological Surgery

Japanese Society of Gastroenterology

Japanese Society of Transplantation

Japanese Society of Hepatology

S4-5

Current Status of Liver Transplantation for HCC in Japan

*Ken Shirabe, Tomoharu Yoshizumi, Toru Ikegami, Shinji Itoh,
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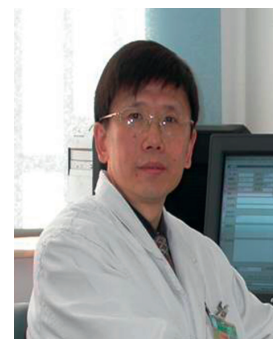
In Japan, because of brain death donor shortage, living donor liver transplantation (LDLT) has been performed in most of the patients with HCC. Milan criteria (MC) is a gold standard for the candidates of liver transplantation (LT) with hepatocellular carcinoma (HCC). In Japan, public insurance has been applied for the patients with HCC within Milan criteria. The outcome of patients with HCC within MC after LT has been reported to be good. Actually, long-term outcome after LT in Kyushu University was extremely good and 5 yr survival after LDLT was beyond 90%, which was significantly better than that of the patients who underwent LDLT for other reasons than HCC. Furthermore, some of the patients with HCC beyond MC have survived without HCC recurrence after LT. Therefore, extension of public insurance for HCC is urgent issue. And in Japan, some of the transplant center has own extended criteria for the patients with HCC beyond Milan criteria. We have proposed Kyushu university criteria, based on tumor size and des-gamma-prothrombin (DCP). In this presentation, extended criteria for HCC beyond Milan criteria in Japan would be introduced.

Session 5

Pathological and Molecular Diversity in HCC

Speaker's Curriculum Vitae

Name Wen-Ming Cong, MD, PhD
Position Professor and Director
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Wen-Ming Cong studied Medicine at the Second Military Medical University and graduated in 1976. Following this, he received his MD degree and Ph.D degree in the same University in 1987 and 1990, respectively. He is currently the Professor and Director of the Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Shanghai since 1996. Now, he also serves the vice-director of Chinese Societies of Liver Cancer of Chinese Anti-Cancer Association.

In 1997, Professor Cong firstly reported the pathologic diagnoses of a series of liver biopsies after liver transplantation in China. Then, as a visiting scholar, he studied transplantation pathology and genetic alterations of hepatic tumors at the Division of Transplantation Pathology, University of Pittsburgh Medical Center in USA from 1999–2000.

From October 2002, Professor Cong serves as the chief of the Chinese Pathology Working Group on Hepatobiliary Tumors and Liver Transplantation. He has pathologically diagnosed ≥40,000 cases of hepatobiliary tumors and 1,400 cases of liver transplantation biopsies. In 2007 and 2009, in the name of Pathology Working Group, he published the papers entitled 'The guideline of pathological diagnosis and classification of common complications after liver transplantation: Part I and II; and in 2015, in the name of Chinese Society of Liver Cancer and Pathology Working Group, he published the papers entitled 'Evidence-based guideline for the pathological diagnosis of primary liver cancer in China (2015 update)'.

Professor Cong received 'the century outstanding academic leader training program of Shanghai healthy system', six times of National Natural Science Foundations of China. He is awarded the third prize of the National Science and Technology Progress Award of China, the first prize of the advances in science and technology of Shanghai government, the first prize of meicial achievements of PLA, and five times of the excellent articles of the Chinese academic meetings. Professor Cong published several books including 'Surgical Pathology of Hepatobiliary Tumors', and 'The Clinicopathology of Liver Transplantation'. He has published more than 200 domestic and international articles.

Professor Cong is interested in the research of genomic instability, clonal origin of recurrent HCC, pathobiological features of small hepatocellular carcinoma.

S5-1

Evidence-Based Guideline for the Pathological Diagnosis of Primary Liver Cancer in China (2015 Update)

Wen-Ming Cong, Sheng-Long Ye, Bu Hong

Chinese Society of Liver Cancer, Chinese Anti-Cancer Association,
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Based on the statistics of the incidence of malignant tumors worldwide released in 2015, hepatocellular carcinoma (HCC) is the malignant tumor that ranks 5 and 9 in incidence as well as 2 and 6 in mortality for males and females, respectively. China is one of the countries with a relatively high HCC incidence. According to the annual reports released by the National Central Cancer Registry of China in 2011, the crude incidence of liver cancer is 28.71/100,000 making it the fourth most common cancer in China, third most common cancer in males, and fifth most common cancer in females. Surgical removal is the primary treatment for liver cancer, while pathology is the main supporting discipline to hepatic surgery. Therefore, seven Chinese Societies organized to formulate the 2015 update of evidence-based guidelines for pathological diagnosis of primary liver cancer, which consists of 5 parts with 12 recommendations. Here, we briefly introduce this pathology guidelines as follows.

Scheme of Pathological Examination:

Recommendation 1: The 7-point sampling method is just a baseline scheme. In actual practice, modification of the specimen sites and numbers should be based on the diameter, shape and number of the tumors, and size of the peritumoral tissue. Furthermore, detection rates of microvascular invasion and satellite nodules are associated with the resection range of the peritumoral tissue. Thus, descriptions should involve peritumoral tissue size and specimens should be sampled for suspicious nidi based on multilevel examinations (C, I).

Key Elements in the Gross Specimen Description:

Recommendation 3: SHCCs ≤ 3 cm tend to manifest relatively benign pathobiological features including good differentiation, expansive growth, and a low incidence of microvascular invasion and satellite nodules, which are an indication for radical intervention. Radical therapy at an early stage before SHCCs exhibit highly aggressive behavior is of tremendous clinical and practical significance in improving PLC patients' long-term prognosis (B, I).

Recommendation 4: SHCC is based on tumor diameter, which is not equivalent to the biological concept of early hepatocellular carcinoma. Malignant features such as poor differentiation, invasive growth, microvascular invasion, and satellite nodule formation may appear in some SHCCs or even micro-hepatocellular carcinomas, indicating that these SHCCs have already advanced to the malignant stage. Therefore, complete specimen sampling of the cancerous tissues of SHCC ≤ 3 cm should be conducted to evaluate the biological behavior (B, I).

Pathological Diagnosis of Microvascular Invasion:

Recommendation 8: MVI is an important predictive marker for the prognoses of patients with liver cancers (A, I); therefore MVI should be counted in all the tissue specimens and graded according to the risk stratification based on the number and distribution of MVI as follows: M0: no MVI; M1 (low-risk group): ≤ 5 MVIs located at the peritumoral tissue zone near the cancer (≤ 1 cm); and M2 (high-risk group): > 5 MVIs, or MVI located at the peritumoral tissue zone far from the cancer (> 1 cm) (B, I).

Immunopathological Diagnosis:

Recommendation 11: CD34 immunochemical staining does not directly label the liver parenchymal cells but is able to demonstrate the density and distribution patterns of microvessels in different liver cancers, for instance, diffuse in HCC, loose in ICC, patchy in hepatic adenoma, and cord-like in hepatic focal nodular hyperplasia, which will facilitate differential diagnosis (B, I).

Molecular Pathological Diagnosis:

Recommendation 12: Clonal origin of multinodular and recurrent liver cancers is vital to developing individualized therapeutic regimens and improving long-term efficacy. Therefore, assessing the clonal origins of liver cancers using molecular cloning will provide objective reference for the development of individualized therapeutic regimen (B, I).

Pathological Diagnosis Report:

Clinical pathology of the liver should be highlighted and the pathological risk factors of postoperative recurrence addressed in the pathological diagnosis report for liver cancers. Pathological features usually comprise gross specimen description, microscopic description, immunochemical results, results of other special examinations, typical pathological pictures, and the specific pathological diagnosis, as well as a necessary note that describes/explains the issues, such as important tumor biology or lesions that require further differential diagnosis clinically. Furthermore, for convenient recording and analysis of clinical and pathological indices, a checklist should be attached after the pathological report, as appropriate.

Speaker's Curriculum Vitae

Name Valérie Paradis, MD, PhD
Position Professor
Institution Department of Pathology, Beaujon Hospital, Clichy France & Université Paris 7, France



Valérie Paradis studied Medicine at University Paris 11, graduated in 1992 and received PhD degree in 1999. Mrs Paradis is currently a Professor at the Department of Pathology, Beaujon hospital and the Team leader 'From inflammation to cancer in Digestive diseases' in the Research Center on Inflammation INSERM (Paris Montmartre).

Chairman in Master M1 & M2 (Mention Cell biology Physiology Pathology, Speciality 'Epithelium : interface structures') and in Pathology (2nd & 3rd cycle medical school).

Elected member of national councils (University, French Research Institute [INSERM, ANRS, Digestive International society (Diseases Working Group for the European Society of Pathology (Secretary, 2011-), ssociation Française de l'étude du Foie (AFEf, Administrative board, 2012-)).

Thematic Research:

V Paradis is involved in basic sciences and clinical research dedicated to liver fibrosis and liver carcinogenesis. The main contributions are related to identification of molecular mechanisms involved in the pathogenesis of benign liver neoplasms, preneoplastic cirrhotic nodules and hepatocellular carcinomas (HCC) using molecular and pathological approaches including in situ proteomics. A specific interest has been developed on HCC associated with metabolic syndrome, showing specific chromosomal abnormalities leading to overexpression of cullin7, an E3-ligase located at the 6p21.1 locus, the amplification of which influence cell apoptosis in functional studies. Translational research projects through the development of proteomic approaches allowed the identification of non invasive diagnostic markers of HCC and tissue biomarkers predictive of vascular invasion (modified forms of Histone H4, PIVKA-II). Significant effort is made on the development of culture of fresh tumor slices aiming to establish predictive models of therapeutic response.

Supervisor of 5 PhD thesis program, and 9 Master internship.

Award: Lauréate de la prime d'excellence scientifique (2009, 2014).

Scientific Activity: (H-index 46).

Author of more than 204 peer reviewed journal articles, 16 book chapters, 1 patent, 75 invited conferences.

S5-2

Hepatobiliary Carcinomas: An Emerging Tumor

Valérie Paradis

Department of Pathology, Beaujon Hospital, Clichy France & Université Paris 7, Paris, France

Primary liver carcinomas encompass a wide range of tumors, from hepatocellular carcinoma to cholangiocarcinomas. In between, mixed (or biphenotypic hepatobiliary carcinomas) are more and more recognized, mainly thanks to the use of immunochemistry. Interestingly, these tumors, at least a large majority of them, allowed to support the concept of hepatic progenitor cell origin in liver malignancies.

The last WHO classification dedicates one chapter to hepatobiliary carcinomas and proposed a revised classification, identifying the classic type and the type with stem cell features. Further studies are needed to validate this morphological classification but mostly to assess its prognostic value. Indeed, whereas older series have reported their poor prognosis, the more recent data are more conclusive.

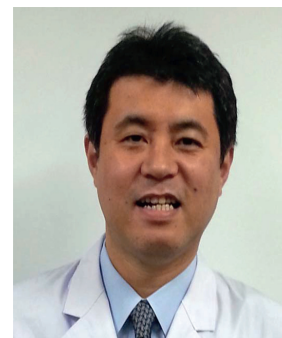
In the field of primary liver carcinomas, significant advances in terms of classification and prognosis have been performed, mainly through molecular analysis. Development of pathomolecular classification might be the next step for a reliable and accurate management of patients with primary liver carcinomas.

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Speaker's Curriculum Vitae

Name Taro Yamashita, MD, PhD
Position Assistant Professor
Institution Department of General Medicine,
Kanazawa University Hospital



Taro Yamashita is a graduate of the Kanazawa University and completed his gastroenterology residency at the Kanazawa University Hospital. He spent three years as a visiting fellow at the Laboratory of Human Carcinogenesis, NCI-Bethesda, MD. He returned to Japan as an Assistant Professor of Department of Gastroenterology in 2008 and then moved to the current position in 2012. He is a member of the American Association of Cancer Research, American Association for the Study of Liver Diseases, The Japan Society of Hepatology, The Japanese Society of Gastroenterology, and The Japanese Cancer Association. He received Young Investigator Travel Award by American Association for the Study of Liver Diseases in 2004, Young Investigator Award by Gastroenterology Research Group/American Gastroenterological Association in 2005, OTSUKA Award by The Japan Society of Hepatology in 2010, Distinguished Research Award by Viral Hepatitis Research Foundation of Japan in 2011, and Invention Prize by Japan Institute of Invention and Innovation in 2013.

His current research interests include the classification of liver cancer based on molecular profiling approaches and the development of novel treatment strategies targeting liver cancer stem cells.

S5-3

Diversity of Cancer Stem Cells in Hepatocellular Carcinoma

Taro Yamashita, Masao Honda, Shuichi Kaneko

Department of General Medicine, Kanazawa University Hospital,
Kanazawa, Japan

Carcinogenesis could be characterized as deregulated malignant organogenesis mediated by abnormally proliferating and/or metastatic cancer cells and activated stromal cells that trigger angiogenesis, fibrosis, and inflammation at site. Liver cancer development may recapitulate fetal liver development in part in terms of emergence of cells expressing certain stem cell markers and the activation of signaling pathways during the liver development. Cancer cells and stem cells have similar capacity in view of self-renewal, limitless division, and generation of heterogeneous cell population. The cancer stem cell (CSC) concept, a subset of cells bearing stem cell features that is indispensable for tumor development and perpetuation, has recently been accepted by accumulating evidences. Although CSCs have been identified using several stem cell markers and are now considered a pivotal target for the eradication of hepatocellular carcinoma, little information is known about the characteristics of each-marker-positive cells. Here we provide several evidences that liver CSCs defined by EpCAM and CD90 show unique features of tumorigenicity/metastasis with phenotypes closely associated with committed liver lineages, indicating that liver CSCs are not a single, static entity. The presence of CD90⁺ cells was associated with high incidence of distant organ metastasis within two years after surgical resection, and CD90⁺ CSCs showed the molecular features of vascular endothelial cells with abundant expression of c-Kit and chemosensitivity to imatinib mesylate. In contrast, the presence of EpCAM⁺ cells was associated with high serum AFP values, high frequency of portal vein invasion, and poor prognosis after surgery, and EpCAM⁺ CSCs showed the molecular features of hepatic stem/progenitor cells with abundant expression of SALL4/HDAC1/CHD4 and chemosensitivity to HDAC/PARP inhibitors. These data suggest that clinical outcomes of liver cancer may correlate with the presence of certain CSCs with distinct biological features. Our studies demonstrate the importance of evaluating stem/maturational status in hepatocellular carcinoma, paving the way toward new treatment strategies for advanced hepatocellular carcinoma patients with poor prognosis.

Speaker's Curriculum Vitae

Name Young Nyun Park
Position Avison Distinguished Professor,
Department of Pathology
Institution Yonsei University College of
Medicine



Professor Young Nyun Park studied medicine at Yonsei University and graduated in 1987, and she earned Ph.D. from Yonsei University College of Medicine in Seoul, Korea, in 1994. Following this, she studied liver pathology at Mount Sinai Medical Center in the U.S. She started her academic career in 1996 as assistant professor and became a professor in the Department of Pathology at Yonsei University College of Medicine, in 2006. She served as the Vice Dean for Research Affairs and Graduate Affairs of Yonsei University College of Medicine from 2008 to 2014. She currently serves as an editorial board member for Hepatology. Professor Park has focused on understanding the early stage of hepatocarcinogenesis and cancer stem cells of hepatocellular carcinoma. She has published about 160 peer reviewed papers in international journals, including Hepatology, Journal of Hepatology, American Journal of Pathology, etc. She has contributed to the sections of hepatocellular carcinoma and combined hepatocellular-cholangiocarcinoma in the 4th edition of WHO Classification of Tumours of the Digestive System in 2010 and the textbook entitled Practical Hepatic Pathology published by Elsevier in 2011. She has received 16 awards, including the best research awards from the Korean Society of Pathologists in 2006, the Korean Association for the Study of the Liver in 2002, Seoul Medical Association in 2013, and Yonsei University in 2010, 2011, 2013 and 2014.

S5-4

HCC with Stemness in Tumor Progression and Microenvironment

Young Nyun Park

Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

Cancer cells in hepatocellular carcinoma (HCC) are heterogeneous, and cancer cells exhibiting stem cell-like features ('cancer stem cells') can be found in HCCs. Recent studies have introduced a new subtype of HCC, which shows a fraction of tumor cells (>5%) expressing stem cell markers but is otherwise not recognizable by routine hematoxylin-eosin stain. HCCs expressing stem cell markers reportedly show more frequent vascular invasion, more fibrous stroma, and more aggressive behavior, compared to conventional HCCs without stem cell marker expression. However, the appearance and role of cancer stem cells in human multistep hepatocarcinogenesis are poorly understood. The expression of liver stem cell markers (EpCAM, K19, Oct3/4, c-KIT, c-MET, LIF, CD133) was investigated in cirrhosis, low-grade dysplastic nodules (DNs), high-grade DNs, early HCCs, and progressed HCCs. The expression of liver stem cell markers showed a gradual increase according to the progression of hepatocarcinogenesis, with a significant increase between early HCCs and progressed HCCs. The protein expression levels of EpCAM and K19 were significantly higher in poorer differentiated and larger HCCs ($P < 0.05$, all). Cancer stem cells are reported to be affected by tumor microenvironment, therefore the tumor stromal cells and TGF- β signature genes were further investigated. The protein expression of α -SMA, marker of tumor stromal cell and the mRNA levels of TGF- β signature genes gradually increased according to the progression of hepatocarcinogenesis ($P < 0.05$, all). Additionally, the expression status of stem cell markers was well correlated with those of α -SMA and TGF- β signature. In conclusion, the cancer stem cells and tumor stromal cells are considered to increase according to progression of multistep hepatocarcinogenesis through the cross-talk, and to be more involved in late hepatocarcinogenesis rather than early hepatocarcinogenesis.

Speaker's Curriculum Vitae

Name Michiie Sakamoto
Position and Institution Professor, Department of Pathology, Keio University School of Medicine
Vice-dean, Keio University School of Medicine, Tokyo, Japan



Education:

1985 M.D., Keio University School of Medicine
1989 D. Med. Sci., Keio University Graduate School of Medicine

Board:

1990 Certified Pathologist of the Japanese Society of Pathology

Brief Chronology of Academic Appointments:

1989– Researcher, Pathology Division, National Cancer Center Research Institute
1996– Head of Section, Pathology Division, National Cancer Center Research Institute
1996–1997 Visiting Research Fellow, The Burnham Institute (Dr. Erkki Ruoslahti)
1999– Chief, Pathology Division, National Cancer Center Research Institute
2002– Professor, Department of Pathology, Keio University School of Medicine
2009– Vice-dean, Keio University School of Medicine

Societies:

The Japanese Society of Pathology (Director)
The Japanese Cancer Association (Councilor)
The Japanese Society of Hepatology (Councilor)
American Association of for Cancer Research
Liver Cancer Study Group of Japan (Permanent Secretary)

Awards and Honors:

2000 Tamiya Memorial Award
2001 The Japanese Society of Pathology, Pathology Research

Editors:

Editor in chief: Pathology International
Associate Editor: Cancer Science, Hepatology Research, Keio Journal of Medicine
Editorial Boards: Japanese Journal of Clinical Oncology, etc.

Specialty and Research Field of Interests:

Molecular Pathology of Cancer (HCC etc.) and Pathology Information

S5-5

Wnt/ β -Catenin Activated Subclass of HCC

Michiie Sakamoto

Department of Pathology, Keio University School of Medicine, Tokyo, Japan

Series of genetic studies indicated that the most frequently mutated oncogene or tumor suppressor gene in HCC is β -catenin. Molecular subclassification based on gene expression signature proposed a typical hepatocyte-like subclass of HCC harboring this gene mutation which showed a more differentiated histology with a less aggressive clinical outcome.

We previously identified that LGR5 is frequently overexpressed in HCC with β -catenin mutation. LGR5 is known as one of the downstream target genes of Wnt signaling pathway, however its functional role in cancer has been largely unknown. We demonstrated that cells transfected with LGR5 established higher colony forming activity, and were more resistant to a cytotoxic drug than cells transfected with empty vector. Overexpression of LGR5 inhibited cell motility. LGR5-transfected cells formed nodule type tumors in the livers of immunodeficient mice, whereas empty vector-transfected cells formed more invasive tumors. These suggest that aberrant expression of LGR5 regulates epithelial cell phenotype and survival of HCC and moreover, represent a typical phenotype of HCC.

We also indicated strong association between OATP1B3 expression and Wnt/ β -catenin signaling in surgically resected clinical samples and in vitro model. It was suggested that tumor enhancement in EOB-MRI predict Wnt/ β -catenin-activated HCC with the sensitivity and specificity of 78.9% and 81.7%, respectively.

It was also indicated that comprehensive immunohistochemical analyses of clinical samples roughly separated the HCCs into 3 groups: biliary/stem cell marker positive group, Wnt/ β -catenin signaling related marker positive group, and biliary/stem cell and Wnt/ β -catenin signaling related markers negative group. These data indicate unique features of Wnt/ β -catenin-activated HCC and it is likely a specific subclass of HCC.

Session 6

The BCLC B Stage: Debate

Speaker's Curriculum Vitae

Name Jordi Bruix, MD
Position Professor of Medicine
Institution University of Barcelona
Director of the Barcelona Clinic
Liver Cancer Group, Liver
University Hospital Clínic of
Barcelona, Barcelona, Spain



Jordi Bruix, MD, is Professor of Medicine at the University of Barcelona and Director of the Barcelona Clinic Liver Cancer Group within the Liver Unit at the Hospital Clínic of Barcelona in Barcelona, Spain.

Dr. Bruix is a member of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). He founded the International Liver Cancer Association and was nominated President from 2006 to 2009. He has been Associate Editor of *Journal of hepatology*, *Liver Transplantation* and *Hepatology*, and is currently Associate Editor of *Seminars in Liver Disease*, while also being reviewer for several journals and official agencies in USA, Europe and Asia.

Dr. Bruix has been principal investigator of studies and clinical trials that have changed practice in the field of HCC, this including development of diagnostic criteria, prognostic models and establishing chemoembolization and sorafenib as conventional therapy. He has developed the BCLC staging and treatment strategy that has been endorsed by several international scientific associations to guide management of patients with HCC. Dr. Bruix has authored more than 150 original investigations and led the Evidence-based Practice Guidelines for Hepatocellular Carcinoma at EASL, AASLD and WGO, as well as consensus statements to define endpoints in clinical trials that have paved the conduct and analysis of such investigations.

S6-1

The BCLC B Debate: Should It Be Stratified? For Practice? For Research?

Jordi Bruix

BCLC Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain

The number of proposals to stratify patients diagnosed with hepatocellular carcinoma according to prognosis is unlimited. The most validated and widely used is the BCLC model. It provides at first a prognosis assessment by taking into account tumor burden, severity of liver disease and the patient's performance status using the ECOG score. After this initial prognosis assessment, each stage is linked to the appropriate treatment as supported by level 1 or 2 evidence. Obviously, not all clinical parameters to reach a treatment decision should be expected to be detailed in any system as physicians are expected to behave as such and personalize treatment approach using additional parameters (comorbidities, technical feasibility, personal values). In that sense, if a patient in a given stage is not fit for the option offered as optimal approach, it is obvious that the patients should be offered the therapy for a later stage. This is known as 'treatment stage migration'. The intermediate stage (BCLC B) comprises asymptomatic patients with multifocal large tumors without vascular invasion or extra-hepatic spread, and in whom liver function is preserved. This definition encompasses a wide range of patients with heterogeneous tumor burden and liver function. Subclassification has been proposed but with key misuse of the BCLC recommendations. It is frequent to see that patients with large solitary HCC (>5 cm) are classified as BCLC B and not as BCLC A, where they belong. Furthermore, liver function evaluation by any expert hepatologist is not simply restricted to Child-Pugh score/class. It is well known that Child-Pugh A or B can include patients with ascites, in whom events such as bacterial peritonitis, hyponatraemia, renal failure or recurrent encephalopathy are predictive of poor outcomes in the absence of transplantation. If such events are registered, the patients should be classified as suffering end-stage liver disease and the sole option that may provide survival advantage is transplantation if tumor burden does not exceed listing criteria. If this is not feasible, the proper BCLC stage is D and best supportive care is the policy to follow.

These comments do not mean that no refinement of stratification is feasible. The key concept is to consider what is the goal of it. In the absence of treatment with adverse effects, the prognosis may not be significantly modified by some of the proposed parameters, but some of them sure should be taken into account to evaluate if TACE treatment may be effective or not (ie. TACE in patients with minor decompensation). If treatment is not to be modified stratification may not be needed., but if the goal is to stratify patients in order to run a trial, then several aspects may be considered: liver function impairment as per bilirubin concentration, AFP values, pattern of progression after earlier therapies. However, this is an investigation decision and thus, to be taken by the investigators of the specific trial.

Speaker's Curriculum Vitae

Name Fabio Piscaglia
Position Assoc. Professor of Internal Medicine
Institution Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy



1997 Complete pass of the *United States Medical License Examination (USMLE)*
1997–1998 *one year period at the University of Goettingen, Germany*, in basic (molecular biology) research in liver fibrogenesis
1998 *Specialization in Internal Medicine* at the University of Bologna, Department of Internal Medicine and Gastroenterology
1998–2002 *PhD program in Ultrasound in Human and Veterinary Medicine*
2000 *General Secretary of the WFUMB* (World Federation of Societies for Ultrasound in Medicine and Biology) congress, held in Florence >2500 attendees
2005–Sept 2014 Assistant Professor at the University of Bologna, Division of Internal Medicine
Sept 2014–current Associate Professor of Internal Medicine, at the University of Bologna. Responsible for the Liver Cancer Outpatient Service in the Unit of Internal Medicine. Awarded the clinical position of high specialization (July 2011) in: 'Integrated Clinical and Experimental Management of Liver Tumors' at the Azienda Ospedaliero-Universitaria di Bologna
Chairman of the Center for Ultrasound in Internal Medicine, where more than 8000 US are carried out yearly, including more than 50 interventional procedures and >400 contrast enhanced ultrasound exams per year for focal liver lesion. Consultant for the Liver Transplant Program and coordinator of the hospital bimonthly Liver Oncology meetings
2012 European (UEMS) Honorary Diploma of 'Transplant Hepatologist'
2008–2011 *Member of the Governing Board of the Italian Association for the Study of Liver Disease*
2011–2013 *President of the European Federation of Societies for Ultrasound in Medicine and Biology* (28 Nations, over 20.000 members)
2011–present Member of the Board of Directors of the International Contrast Ultrasound Society (ICUS)
2009 Director of the Euroson School on Contrast Enhanced Ultrasound in Liver, Biliary, Pancreatic and Gastrointestinal Disease, Bologna Sept 16–18
2013 Promoter and member of the steering committee and senior author of the EFSUMB Guidelines and Recommendations on the clinical use of ultrasound Elastography. Part 1, Technology (Ultraschall Med, in press April 2013) and Part 2, Clinical (Ultraschall Med, in press June 2013)
2013 Winner of a Marie Curie action program from the European Union as responsible of one of the 3 centers submitting the application (University of Bologna, University of Barcelona, Yma from Barcelona as Small Industry)
Articles in PubMed 183. (>50 as first author). Total Impact Factor >600 (ISI 2010), more than 3500 citations. H-index 32
Peer reviewer for several (>15) international scientific journal with an Impact Factor >1
Invited speaker at international events on liver tumors and liver disease with over 100 lectures
July 2013–current Associate Editor of Ultraschall in der Medizin/European Journal of Ultrasound (IF 4.65 as of 2014)

Research Interest:

Hepatocellular carcinoma, Diagnosis of HCC, Abdominal ultrasound

S6-2

Should Be Stratified: Prognosis and Treatment Algorithms of Intermediate HCC Patients

Fabio Piscaglia, Veronica Salvatore, Giulia Negrini

Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

The intermediate stage of hepatocellular carcinoma (HCC) by the Barcelona Clinic Liver Cancer (BCLC) staging system is defined as patients with large multinodular HCC (in other words patients beyond the Milan criteria) in Child-Pugh either A or B class with no tumor related symptoms and without extrahepatic spread or macrovascular invasion (altogether defined as BCLC-B). Thus, it comprises a highly heterogeneous patient population, since patients may greatly vary according to both liver function (from perfectly preserved to refractory ascites or jaundice) and tumor burden (from two small nodules, just slightly beyond 3 cm to multiple large- or even huge-HCC involving the largest part of the liver). Consequently, this tumor stage poses unique challenges for prognostication and therapeutic management, different from the early and advanced stages.

Transarterial chemoembolization (TACE) is currently recommended as the standard of care in this setting, but there is considerable variation in the clinical benefit patients derive from this treatment. A balance, in fact, should always be made between antitumor treatment, which in some instance would require extensive interventions and the possible detrimental effects of treatment on hepatic function, especially when function is already partially compromised by the underlying cirrhosis, as such worsening may overcome any oncologic benefits.

In the last decade, after the appearance of the metanalysis of Llovet et al in 2003 showing survival benefit with TACE in unresectable HCC (not always corresponding to intermediate HCC) other works and techniques have emerged, with a potential in the treatment of intermediate HCC. Extended criteria for liver transplantation for HCC, either preceded or not by a downstaging protocol, have been shown to be feasible with good results. Transarterial embolization with Yttrium90 was shown to be more effective than conventional TACE in large HCC. In selected situation surgical resection may also be considered in intermediate stage patients with limited number of nodules (2–3 nodules, with a dominant one) and a forecast for limited parenchymal sacrifice. At last also systemic treatment with Nexavar was demonstrated to provide the same magnitude of survival benefit in the intermediate HCC stage as it does in the advanced stage, according to a subgroup analysis of the randomized controlled registration trial (SHARP).

Accordingly, in April 2012, a panel of European experts convened to discuss unresolved issues surrounding the application of current guidelines when managing patients with intermediate HCC. The meeting explored the applicability of a subclassification system for intermediate HCC patients to tailor therapeutic interventions based on the evidence available to date and expert opinion. Their opinion was published in November 2012 in *Seminars in Liver Disease* (Bolondi L et al, *Sem Liv Dis*, 2012;32:348–359). Four new substages of intermediate HCC patients, B1 to B4, were proposed to facilitate treatment allocation, considering tumor bulk and specific Child-Pugh scores, progressing from B1 to B4 in terms of both conditions, tumor bulk and specific Child-Pugh scores. As expected the treatment allocation had TACE as the mainstay of treatment, but different strength of evidence in the four substages and with possible alternatives to be tailored according to the individual patient conditions. Although statistical meaningful differences among the four substages survivals were not fully reached in a recent analysis of 254 BCLC-B patients analyzed in Germany (Weinmann A et al, *Liver Int*. 2015;35:591–600) a clear trend was evident for survival. In particular groupwise comparison showed significant differences between B1 vs. B3 ($P = 0.035$), B1 vs. B4 ($P = 0.006$) and B2 vs. B4 ($P < 0.0001$).

Once TACE is decided to be performed, what still remains incompletely clarified is the repetition strategy. Various strategies have been proposed, but not well validated out of the proposing centers. What remains widespread accepted is that TACE is repeated only after demonstration of persistent viable tumor after the first session. No TACE repetition is recommended after radiological complete necrosis and recurrence takes place.

Speaker's Curriculum Vitae

Name Chung-Kwe Wang
Position Chairman, Dept. of Internal
Medicine Deputy Superintendent,
Ren-Ai Branch
Institution Taipei City Hospital, Taipei, Taiwan



Chung-Kwe Wang is currently the President of Taiwan Liver Cancer Association (TLCA). He founded the Taiwan Liver Cancer Study Group in 2000 and changed the name as TLCA in 2008.

He is the Chairman at the Department of Internal Medicine, Taipei City Hospital since 2005. He was the Chief of Division of Gastroenterology and Hepatology of Department of Internal Medicine from 2005 to 2009. He is a Clinical Associate Professor of National Yang-Ming University and Lecturer of Taipei Medical University since 2009.

Dr. Wang graduated from China Medical University at Taichung, Taiwan. After finished his resident and fellowship training at Taipei Municipal Ren-Ai Hospital, he went to Nihon University and Kurume University to study liver pathology. He was a Visiting Scientist at Laboratory of Molecular Oncology in National Cancer Institute, USA, from 1992 to 1993. He got his Master Degree at Department of Health Policy and Management, Johns Hopkins University in 2005.

Dr. Wang has published many international scientific peer review papers in well regarded journals and domestic scientific papers. He serves as the Board Member of Gastroenterology Society of Taiwan and Manuscript Reviewer of Journal of Gastroenterology and Hepatology and Journal of Cancer Research and Practice.

Research Interest: Hepatology, Liver Pathology, Molecular Oncology

S6-3

Treatment Choice of Intermediate Stage HCC: Surgical Resection or TACE

Chung-Kwe Wang

Department of Gastroenterology and Hepatology, Ren-Ai Branch, Taipei City Hospital, Taipei, Taiwan

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. More than 75% of HCC cases occur in the Far East and Southeast Asia. Only a small proportion of patients have their HCC detected in an early curable stage, thus the worldwide 5-year survival rate of HCC only slightly increased from 5 to 15% over the past two decades. Current guidelines recommend transarterial chemoembolization (TACE) as the standard treatment for patients with intermediate stage hepatocellular carcinoma (HCC). However, choosing the optimal treatments for patients with intermediate stage HCC still remains challenging for clinicians.

In our previous study with 123 newly diagnosed intermediate stage HCC patients treated solely with TACE, The 1-year to 5-year overall cumulative survival rates were 65.9%, 46%, 33.2%, 22% and 18.4%, respectively. Multivariate analysis revealed that AFP level >400 ng/ml [hazard ratio (HR): 2.663, 95% CI: 1.143–6.205, $P = 0.023$], CTP class B cirrhosis (HR: 4.69, 95% CI: 1.399–15.715, $P = 0.012$) and tumor size (HR: 1.153 for each 1 cm increase, 95% CI: 1.015–1.310, $P = 0.029$) were independently associated with one year mortality (Lin CL & Wang CK et al. *Advances in Digestive Medicine* 2014;1:126–131). Our study indicated that the long-term effects of TACE for intermediate stage HCC still remain unsatisfactory.

Recent advances in liver surgery make the resection of intermediate stage HCC possible. This prompted us to compare the long-term survival of intermediate stage HCC patients treated with surgical resection or TACE. A total of 210 intermediate stage HCC patients were recruited for this study. There were 164 men and 46 women, with a mean age of 63 ± 11 years (range, 31 to 92 years). Among them, 67 patients (31.9%) received surgical resection and 143 patients (68.1%) received TACE. Patients receiving surgical resection had a significantly larger mean of maximum tumor size (6.8 ± 2.8 vs. 5.8 ± 3.2 cm, $P = 0.016$), higher ratio of solitary tumor (68.7% vs. 17.5%, $P < 0.001$), and Child-Pugh class A (97% vs. 85%, $P = 0.009$) than those with TACE. Patients receiving surgical resection had a significantly higher 1, 3, and 5 year survival rate compared with those treated with TACE (87.4%, 62.8% and 57.3% vs. 58.1%, 29.9% and 16.6%, $P < 0.001$). Multivariate analysis revealed that AFP level >400 ng/ml [hazard ratio (HR): 2.141, 95% CI: 1.091–4.203, $P = 0.027$], Child B cirrhosis (HR: 4.726, 95% CI: 1.021–21.884, $P = 0.047$), and TACE (HR: 3.391, 95% CI: 1.625–7.076, $P = 0.001$) were independent risk factors associated with poor prognosis (Lin CL & Wang CK et al. *Journal of Cancer Research and Practice*, in press).

In conclusion, our results indicated that surgical resection provided superior survival benefit than TACE to patients with intermediate-stage HCC. This is in part attributable to advances in liver surgery which make the resection of intermediate-stage HCC possible. Surgical resection should be considered first for patients with preserved liver function.

Speaker's Curriculum Vitae

Name Joong-Won Park
Position Principal Scientist
Professor
Institution Center for Liver Cancer, National
Cancer Center, Seoul, Republic of
Korea



Joong-Won Park is a Principal Scientist of the National Cancer Center, Korea and a Professor of Graduate School of Cancer Science and Policy, NCC Korea. He was the Head of the Center for Liver Cancer, NCC, Korea from 2002 to 2010, and was the Head of Translational and Clinical Research at the National Cancer Center Research Institute from 2008 to 2011. Dr. Park completed his Medical degree at Seoul National University in 1984 followed by a residency in Internal Medicine and a Clinical Fellowship in Hepatology at Seoul National University Hospital. He completed a PhD in Medicine at Seoul National University in 1996. He was an Assistant and Associate Professor of Chung-Ang University Medical College from 1993 to 2002 and was a Visiting Scientist at the Center for Basic Research in Digestive Diseases, Mayo Clinic, Rochester, USA, from 1997 to 1999. Dr. Park has published extensively in both International and Korean journals and given many invited lectures on hepatitis and liver cancer. He serves as Chair of the Committee for the Hepatocellular Carcinoma Management Guidelines of the Korea Liver Cancer Study Group (KLCSG)-NCC Korea and is a member of the Korean Association for the Study of the Liver (KASL), the Asian-Pacific Association for the Study of the Liver (APASL), the American Association for the Study of Liver Diseases (AASLD), and the International Liver Cancer Association (ILCA). He served as Chair of the Scientific Committee for the APASL 2008 Seoul meeting, a Chair of the Scientific Committee of the KASL from 2003 to 2005, and as Chair of the Scientific Committee of the KLCSG from 2002 to 2004. Dr. Park's research interests are the management of hepatocellular carcinoma, molecularly targeted therapy, and hepatocarcinogenesis.

S6-4

Transarterial Chemoembolization Refractoriness

Joong-Won Park

Center for Liver Cancer, National Cancer Center, Seoul, Korea

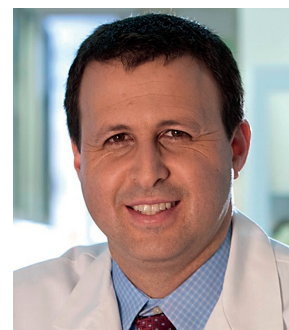
According to current guidelines of most countries, the consensus for standard care for unresectable intermediate stage hepatocellular carcinoma (HCC) is transarterial chemoembolization (TACE). However, the Barcelona Clinic Liver Cancer (BCLC) staging criteria for intermediate stage includes a wide range 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.

Session 7 Systemic Therapy I

Speaker's Curriculum Vitae

Name Richard S. Finn, MD
Position Associate Clinical Professor
Institution Department of Medicine
UCLA David Geffen School of
Medicine, University of California,
Los Angeles, CA, USA



Dr. Finn is an Associate Clinical Professor of Medicine at the UCLA David Geffen School of Medicine in the division of Hematology/Oncology and co-director of the Signal Transduction and Therapeutics Program in the Jonsson Comprehensive Cancer Center at UCLA. He attended medical school at the University of Southern California (USC) then returned to UCLA for his clinical training in Internal Medicine and Hematology/Oncology and has been on faculty since completing his training in 2003.

He currently splits his time between patient care and laboratory and clinical research. His research interests lie in the development of molecular targeted agents and biomarkers in cancer. Dr. Finn has served as principal investigator in several trials exploring the use of targeted therapies in breast and liver cancers. His work has been published in the *Journal of Clinical Oncology*, *Nature Medicine*, *Lancet Oncology*, *Cancer Research*, and *Clinical Cancer Research* and among other journals. He is currently president-elect of the International Liver Cancer Association (ILCA).

S7-2

Understanding Failures in Phase III Studies in HCC: Lessons Learned

Richard S. Finn

Department of Medicine, UCLA David Geffen School of Medicine,
University of California, Los Angeles, CA, USA

Numerous studies have identified that HCC does not represent a single disease entity but represents a molecular diverse disease. This observation is not unique to HCC, but unlike other malignancies, at the current time this molecular diversity has not been incorporated into the management of patients. It can be argued, the greatest impact in the management of patients with cancer, has come from the linking of a biologic alteration to a therapeutic intervention. Since sorafenib's approval in 2007, no other systemic agent has been shown to be effective in the management of patients with advanced HCC. Instead, we have seen repeatedly negative large Phase III studies in both the front-line and second-line setting. Clearly something needs to change in how we conduct studies in HCC or we will continue to see negative results. Most studies to date have taken an 'all comers' approach, selecting patients based on their clinical stage of disease but not on any specific predictive marker for response. Moving forward, enriching for a patient population that is more likely to benefit from a given intervention/therapeutic will minimize the risk of failure in the future. This does not only mean biomarker selection but clinical selection factors as well. As we have seen, after the approval of sorafenib, survival in the second-line setting has been very heterogeneous and clinical selection factors need to be refined as well. In the presentation we will review what we have learned from the Phase III failures and how to mitigate negative trials in the future.

Speaker's Curriculum Vitae

Name Ann-Lii Cheng
Position Professor and Department Chair
Institution National Taiwan University
Hospital, Taipei, Taiwan



Ann-Lii Cheng is Professor and Chairman of the Department of Oncology of the National Taiwan University Hospital in Taipei, Taiwan. He received his MD degree, PhD degree, and his specialty training in Medical Oncology at the Medical School of the National Taiwan University. In 1990, he was a research fellow at the Comprehensive Cancer Center of the University of Wisconsin, Madison, USA. Dr. Cheng has been actively involved in basic and translational research in hepatocellular carcinoma and has published more than 200 peer-reviewed articles. He received the 'Outstanding Research Award' from the National Science Council of Taiwan, and the 'Outstanding Cancer Research Award' from the Chinese Oncology Society. He became 'Distinguished Professor' of National Taiwan University in 2006, and was elected as Fellow of American Association for the Advancement of Science (AAAS) in 2007. Dr. Cheng is an active member of the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). He has served on the editorial boards of *Oncology (Basel)*, *Asia-Pacific Journal of Clinical Oncology*, and *Targeted Oncology – Biotherapies for the Clinicians in Oncology*. In addition, Dr. Cheng is Chairman of the Chemotherapy Committee of the Taiwan Cooperative Oncology Group, of which he was one of the founding members. He received the national award of 'outstanding contributions for science and technology' in 2008, and a national award for academic excellence in 2010. He served as president of the Taiwan Oncology Society during 2009–2011. He was elected as National Professorship Taiwan 2013.

Research Interest: Translational research for endemic cancers of Asia-Pacific region.

S7-3**Combining Adaptive Design and Omics for Future HCC Trials***Ann-Lii Cheng*

National Taiwan University Hospital, Taipei, Taiwan

Adaptive trial design is defined as ‘prospectively planned opportunity for modification of one or more specified aspects of the study design based on interim analysis of a study’ (FDA draft guidance 2011). One simplest form, ‘group-sequential design’, which allows for early stopping in the instance of clearly established efficacy or futility, has been adopted by most modern phase III trials, including the seminal SHARP study. Another adaptive trial design, ‘biomarker-adaptive design’, in which the biomarker response at interim analysis can be used to determine which target population should be focused on, has become popular in oncology trials. Some sophisticated modern biomarker adaptive trials, such as I-SPY I and I-SPY II for breast cancer, and BATTLE I and BATTLE II for lung cancer are simultaneously testing multiple drugs and multiple biomarkers. These trials have also adopted Bayesian design to continuously re-adjust randomization ratio, a practice allows for the better-performing drug-marker couples to enroll more patients. Early experiences of these trials are encouraging.

Recently, adaptive design has been pushed to its extreme. In these extreme adaptive designs, such as the ‘master protocol’ for second-line squamous non-small cell lung cancer (NSCLC), an ‘open-listed’ drugs from different pharmaceutical companies are tested in one umbrella protocol which consists of multiple seamless phase II/III trials, with the goal of getting FDA approval within shortest time possible. Therefore, the design concept is completely different from that of conventional trials. These ‘super-adaptive’ trials are actually ‘living’ and ‘growing’, as the number of patients and the number of drugs are not fixed.

Apparently, operating a ‘super-adaptive’ trial such as the master protocol for squamous NSCLC takes a huge effort, which should manage to coordinate government agencies, multiple pharmaceutical companies, and a highly capable data-managing center. Is it time for HCC trials to move into this direction? Similar to squamous NSCLC, there are many druggable targets rapidly being identified in HCC. Testing these targets one by one will be not only costly and time consuming, but also frustrating and less attractive, as many of the biomarkers will be positive in less than 10% of the patients. This is particularly painstaking in HCC, because biopsy is not routinely required for diagnosis. Even for those with archived tissues, biopsy may still be needed because clonality of the recurrent tumors is often altered. A ‘master protocol’ – like design will provide the highest chance for biopsied patients to be enrolled in trials that are testing drug most biologically relevant to their diseases. However, in the light of current situation of drug development for HCC, it is unlikely that any existing body is able to organize a study of similar magnitude. At the moment, a smaller-scale attempt, such as cluster-by-cluster studies, with each cluster testing 3–4 drugs from one or two companies, appears more realistic. However, before we try to move into this direction, the society should reach consensus regarding what biomarker signatures and what biomarker assays are considered mature.

Speaker's Curriculum Vitae

Name Josep M. Llovet, MD
Position and Institution Professor of Research-ICREA
Director of the Liver Cancer Program and Full Professor of Medicine
Professor, Liver Cancer Translational Research Laboratory, Barcelona-Clínic Liver Cancer Group, IDIBAPS, Hospital Clínic de Barcelona, Universitat de Barcelona (UB), Barcelona, Catalonia, Spain



Josep M. Llovet is **Professor of Research-ICREA** in the BCLC Group, Liver Unit, IDIBAPS-Hospital Clínic de Barcelona (Spain), **Director of the Liver Cancer Program and Full Professor of Medicine** at the Mount Sinai School of Medicine, New York University (USA), and **Professor** at Faculty of Medicine, University of Barcelona. Professor Llovet obtained his degree in Medicine and Surgery from the University of Barcelona in 1986 and his PhD from the Autonomous University of Barcelona in 1995.

Professor Llovet has been **President of the International Liver Cancer Association (ILCA)** and Chairman of the European Clinical Practice Guidelines of management of liver cancer (EASL-EORTC). He has published more than 220 articles in peer-reviewed journals such as *New England Journal of Medicine*, *Nature*, *Nature Genetics*, *Lancet*, *Cancer Cell*, *Journal Clinical Investigation*, *Journal of Clinical Oncology*, *Lancet Oncology*, *Gastroenterology* and *Hepatology* (total citations 33.629, total impact factor 2234; **h index 77**), more than 40 chapters of books, and has delivered more than 450 lectures. He is Senior Editor of *Clinical Cancer Research*. He is Director of the Official Master in Translational Medicine at the University of Barcelona.

During the last 20 years, Dr. Llovet received the AACR-Landon International Award (2009), the International Hans Popper award (2012), Premi Josep Trueta (2013) and is leading international projects with competitive funding from the European Commission (FP7-HEALTH, HEPTROMIC, 2010) and the US National Institute of Health (R01, 2008). Below, find described the scientific and managerial positions and the main scientific achievements obtained. He has contributed to advancing knowledge in the following areas:

Main Achievements

1. **Clinical classification of HCC:** with the acronym BCLC (Barcelona-Clínic Liver Cancer) classification, first published in Llovet, *Semin Liv Dis* 1999, and then further modified in Llovet, *Lancet* 2003; Llovet, *J Natl Can Inst*, 2008 and Forner, *Lancet* 2012. This classification has been adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.
2. **Establishment of sorafenib as standard of care** in patients with advanced HCC (Llovet, *New Engl J Med* 2008). This breakthrough achievement establishes sorafenib as first line treatment for advanced HCC, and represents the first identification of survival advantages with systemic treatments. Identified by *Nature Medicine* as the most cited paper in oncology 2008–2010. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.
3. **Molecular classification of HCC and intrahepatic cholangiocarcinoma:** A final proposal of a molecular classification of HCC and ICC is based on the results reported in different publications (Wurmbach, *Hepatology* 2007; Hoshida, *New Engl J Med*, 2008, Chiang, *Cancer Res*, 2008; Hoshida, *Cancer Res* 2009, Villanueva, *Gastroenterology* 2011; Sia, *Gastro* 2013, Hoshida, *Gastroenterology* 2013).
4. **Identification of drivers of oncogenesis as targets for therapies.** Several studies led to the identification of **mTOR pathway** [Villanueva *Gastroenterology*, 2008], **Ras pathway** (Newell, *J Hepatol* 2009), **EGFR pathway** (Keng, *Nature Biotech* 2009), **IGF pathway** ([Tovar, *J Hepatol*, 2011], **Wnt Pathway** (Lachenmeyer, *CCR* 2012), **Notch pathway** (Villanueva, *Gastroenterology* 2012), AEG (Yoo, *J Clin Invest* 2009). **miRNAs** (Viswanathan, *Nat Genetics* 2009, Toffanin, *Gastroenterology* 2011) and **FGF19** as drivers of hepatocarcinogenesis and potential targets for therapies. Regarding ICC, discovery of **FGFR2 fusions** and **ARAF** mutations as drivers of tumor progression.

Other Important Achievements

1. **Establishment of chemoembolization as standard of care** in patients with intermediate HCC. Evidence-based establishment through randomized controlled trials [Llovet, *Lancet* 2002] and meta-analysis [Llovet, *Hepatology* 2003] of chemoembolization as standard of care in patients with intermediate HCC. Adopted by American (AASLD) and European (EASL-EORTC) guidelines of management of HCC.
2. **Guidelines of management of HCC:** Chair of EASL-EORTC Guidelines, 2012 (*J Hepatol*, 2012, *Eur J Cancer* 2012), and committee member of guidelines of EASL (2001). Leading author of AASLD guidelines for design of clinical trials in HCC (Llovet, *J Natl Cancer Institute*, 2008).
3. **Establishment of a molecular diagnosis of HCC:** Gene-set (3 genes) based diagnosis of HCC reported in Llovet, *Gastroenterology* 2006, and included in EASL-EORTC guidelines.

S7-4

Molecular Therapies for HCC: Current and Future Direction

Josep M. Llovet^{1–3,*}

¹Liver Cancer Translational Research Laboratory, Barcelona-Clínic Liver Cancer Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic de Barcelona, Universitat de Barcelona (UB), Barcelona, Catalonia, Spain; ²Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Ichan School of Medicine at Mount Sinai, New York, N.Y., USA; ³Institució Catalana de Recerca i Estudis Avançats, Barcelona, Catalonia, Spain

Hepatocellular carcinoma (HCC) is a major health problem. Mortality owing to liver cancer has increased in the past 20 years, with recent reports disclosing an incidence of 780,000 cases/year. Most patients with hepatocellular carcinoma (HCC) are still diagnosed at intermediate or advanced disease stages, where curative approaches are often not feasible. Among the treatment options available, the molecular targeted agent sorafenib is able to significantly increase overall survival in these patients. Thereafter, up to 7 randomized phase III clinical trials investigating other molecular therapies in the first-line and second-line settings have failed to improve on the results observed with this agent. Potential reasons for this include intertumor heterogeneity, issues with trial design and a lack of predictive biomarkers of response. During the past 5 years, a substantial advance in our knowledge of the human genome has provided a comprehensive picture of commonly mutated genes in patients with HCC. Genomic-profiling studies have enabled the classification of hepatocellular carcinoma based on common molecular traits, with mutations in the TERT promoter, CTNNB1 and TP53 as the most frequent alterations. This knowledge points toward specific drivers as candidate for *druggable* therapies (MET signaling, FGF19, VEGF-A). Nonetheless, it has not yet influenced clinical decision-making or current clinical practice guidelines. Thus, progressive implementation of proof-of-concept and enrichment might improve results in clinical trials testing of molecular targeted agents.

Speaker's Curriculum Vitae

Name Chih-Hung Hsu, MD, PhD
Position Associate Professor
Institution Graduate Institute of Oncology,
National Taiwan University College
of Medicine; Department of
Oncology, National Taiwan
University Hospital, Taipei, Taiwan



Dr. Chih-Hung Hsu received his M.D. and Ph.D. degrees in 1990 and 2002, respectively, from National Taiwan University (NTU), Taipei, Taiwan. He finished his post-doctor training between 2002 and 2004 at the Department of Pharmacology, Yale University School of Medicine, CT, USA. Dr. Hsu is a board-certified medical oncologist, and is currently an associate professor of Graduate Institute of Oncology, NTU College of Medicine, Taipei, Taiwan. Dr. Hsu has been serving as the Associate Secretary General of COS, the leading Association of medical oncologists in Taiwan, since 2007.

The major research interest of Dr. Hsu has been the clinical study and translational research of gastrointestinal malignancies, especially liver cancer. He first authored several phase II studies of novel combination strategies, including anti-angiogenic therapy plus metronomic chemotherapy and anti-angiogenic therapy plus an epidermal growth factor inhibitor, in advanced HCC. He published clinical researches that help understand the heterogeneity of advanced HCC patients with variable prognoses, and biomarker studies that help reveal potential prognostic and predictive markers of anti-angiogenic therapy for advanced HCC patients. Dr. Hsu has also served as *ad hoc* reviewers of *International Journal of Radiation Oncology · Biology · Physics (the Red Journal)*, *Journal of Thoracic Oncology*, *Journal of Gastroenterology and Hepatology*, *Asia-Pacific Journal of Clinical Oncology*, *Liver International*, *World Journal of Gastroenterology*, and *Journal of the Formosan Medical Association*.

Research Interest: Clinical and translational researches of advanced HCC.

S7-5

Post-Sorafenib Survival in Hepatocellular Carcinoma Patients

Chih-Hung Hsu

Graduate Institute of Oncology, National Taiwan University College of Medicine, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

Hepatocellular carcinoma (HCC) is a heterogeneous disease with highly variable prognosis even among patients categorized in the same clinical stage. Sorafenib is currently the only approved therapy for advanced HCC. Understanding the post-sorafenib progression/discontinuation survival is important not only for patient management, but also for designing clinical trial of 2nd-line therapy.

In an early study, we retrospectively reviewed 194 advanced HCC patients (91% Barcelona Clinic Liver Cancer [BCLC] stage C, 70% hepatitis B surface antigen-[+], and all with Child-Pugh [CP] class A) who had been enrolled into 1st-line anti-angiogenic systemic therapy between 2005 and 2011. The median survival of the entire group of patients after failing 1st-line therapy was 4 months. We found several factors which were significantly associated with their survival after failing first-line therapy, including CP class [reflecting liver function reserve], performance status [reflecting host condition], Cancer of the Liver Italian Program (CLIP) score, serum alpha-fetal protein (AFP) level, and presence of macrovascular invasion [reflecting tumor burden], and time-to-progression [reflecting tumor behavior under 1st-line therapy]. As expected, only ~50% of the entire group of patients were potentially eligible for 2nd-line clinical trials, and these potential candidates for 2nd-line trials had significantly longer survival time than those who were not (median, 7.8~8.6 months vs. 1.7~2.1 months).

Four studies specifically addressing the survivals after progressing or discontinuing sorafenib treatment in HCC patients have been published. All studies except one are based on single-institute experience. As summarized in the Table, these studies vary in their criteria of starting sorafenib as first-line therapy for HCC, and in their criteria of defining sorafenib progression or discontinuation. Despite of these limitations, these studies reveal several common factors which are of significant prognostic impact in HCC patients who have progressed or discontinued from sorafenib treatment, including those reflecting liver function reserves (such as CP class and bilirubin level), host condition (such as PS and hepatitis C virus-[+]), and tumor burden (new extrahepatic metastasis and AFP level).

The above-mentioned studies also demonstrated that post-sorafenib HCC patients who were potentially eligible for 2nd-line trials had improved post-sorafenib survival, with a median ranging from 5.3 to 13.6 months. They also found several prognostic factors, including PS, reasons of discontinuing sorafenib, MVI, and new EHM. Such prognostic factors, i.e., those of post-sorafenib HCC patients who are candidates for 2nd-line clinical trials, are critically important for the design and interpretation of 2nd-line clinical trials of HCC. Further studies using prospective patient cohorts are warranted to validate these potential prognostic factors.

	Reig et al. (Spain)	Iavarone et al. (Italy)*	Okuyama et al. (Japan)	Lee et al. (Taiwan)
Eligibility for sorafenib as first-line therapy	CP A and B7; PS 0-1; BCLC B or C.	PS 0-2; BCLC B or C.	N.R.	CP A; PS 0-2; BCLC C.
BCLC stage for sorafenib treatment	B (52%) C (48%)	N.R.	N.R.	B (0%) C (100%)
Definition of post-sorafenib population	Radiologic PD	PD (47%), AE (30%), LD (23%)	PD (86%) or AE (14%)	PD (including LD) (93%); AE (7%)
Patient No.	85	260	111	102
HCV/ HBV/alcoholism	57% 12% 25%	60% 16% 7%	62% 18% N.R.	34% 57% 7%
BCLC stage after sorafenib	N.R.	B (8%) C (74%) D (18%)	B (19%) C (58%) D (23%)	N.R.
Post-sorafenib median survival (months)	9.8	4.1	4.8	4.6
Independent prognostic factors for post-sorafenib survival	BCLC stage, PS, CP class, Progression pattern	PS, Prothrombin time, MVI, EHM, AFP $\geq$ 400	HCV, Ascites, Prior therapy, Bil $\geq$ 2, AFP $\geq$ 1,000	PS, CP class, Bil >1.2, PD within 4 months, New EHM

AE = Adverse event; AFP = alpha-fetal protein; BCLC = Barcelona Clinic Liver Cancer; Bil = bilirubin; CP = Child-Pugh; EHM = extrahepatic metastasis; HBV = hepatitis B virus; HCV = hepatitis C virus; LD = liver decompensation; MVI = macrovascular invasion; No. = number; N.R. = not reported; PD = progressive disease; PS = performance status.

* In this study, patients receiving liver transplantation or 2nd-line therapy were excluded from analysis.

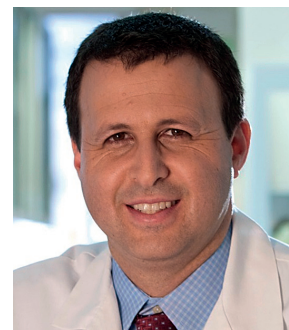
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Session 8 Systemic Therapy II

Speaker's Curriculum Vitae

Name Richard S. Finn, MD
Position Associate Clinical Professor
Institution Department of Medicine
UCLA David Geffen School of
Medicine, University of California,
Los Angeles, CA, USA



Dr. Finn is an Associate Clinical Professor of Medicine at the UCLA David Geffen School of Medicine in the division of Hematology/Oncology and co-director of the Signal Transduction and Therapeutics Program in the Jonsson Comprehensive Cancer Center at UCLA. He attended medical school at the University of Southern California (USC) then returned to UCLA for his clinical training in Internal Medicine and Hematology/Oncology and has been on faculty since completing his training in 2003.

He currently splits his time between patient care and laboratory and clinical research. His research interests lie in the development of molecular targeted agents and biomarkers in cancer. Dr. Finn has served as principal investigator in several trials exploring the use of targeted therapies in breast and liver cancers. His work has been published in the *Journal of Clinical Oncology*, *Nature Medicine*, *Lancet Oncology*, *Cancer Research*, and *Clinical Cancer Research* and among other journals. He is currently president-elect of the International Liver Cancer Association (ILCA).

S8-1

Emerging Therapies in HCC

Richard S. Finn

Department of Medicine, UCLA David Geffen School of Medicine,
University of California, Los Angeles, CA, USA

We are all well aware of the challenge of improving survival in patients with HCC. Since 2007, sorafenib has been the only systemic agent that has a proven survival benefit in advanced HCC. This sobering fact is not the result of a lack of trying. There have been great efforts in the clinical development of new agents but they have unfortunately all failed in Phase III development. Still, despite these challenges, there remains a strong commitment to the development of new agent sin HCC. The future successes will require us to return to our understanding of the pathogenesis of HCC and make stronger efforts into incorporating this knowledge into clinical trials. Novel agents in early development will be explored including immunotherapy, TGF-beta antagonists, and new FGFR inhibitors.

Speaker's Curriculum Vitae

Name Pei-Jer Chen

Position and Institution Professor of Medicine, Graduate Institute of Clinical Medicine, Medical College, National Taiwan University

Professor of Medicine, Graduate Institute of Microbiology, Medical College, National Taiwan University

Distinguished Chair Professor, National Taiwan University, Taipei, Taiwan



Present Positions:

- ◆ Professor of Medicine
Graduate Institute of Clinical Medicine, Medical College, National Taiwan University (1994/09~).
- ◆ Professor of Medicine
Graduate Institute of Microbiology, Medical College, National Taiwan University (1993/08~).
- ◆ Distinguished Chair Professor
National Taiwan University (2006~).

Appointment:

- 1986–1987 Post-doctoral fellow, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University.
- 1987–1993 Associate Professor, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University.
- 1993– Professor, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University.
- 2001–2003 Director, Hepatitis Research Center, National Taiwan University Hospital.
- 2003–2009 Chairman, Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University.
- 2005–2009 Director, Department of Medical Research, National Taiwan University Hospital.

Education:

- 1974–1981 M.D., Department of Medicine, College of Medicine, National Taiwan University.
- 1984–1987 Ph.D., Department of Pathology, Medical School, University of Pennsylvania.

Professional Training and Appointment:

- 1992– Attending Physician, Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital.
- 1991–1992 Fellow, Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital.
- 1987–1990 Resident, Department of Internal Medicine, National Taiwan University Hospital.
- 1983 ECFMG certificate.
- 1980–1981 Intern, National Taiwan University Hospital.

Editorial Appointment:

- 2011– Associate Editor, Liver cancer.
- 2001–2006, Editorial Board, Hepatology, USA.
- 2009–2011 Editorial Board, Hepatology, USA.
- 2001–2002 Editorial Board, Journal of Gastroenterology, Japan.
- 1993–1998 Associate Editor, Proceedings of National Science Council (Biology).

Honors:

- ◆ Member, Academia Sinica, since 2006
- ◆ International Research Scholar (2000–2005) of Infectious Disease, Howard Hughes Medical Institute, US
- ◆ National Outstanding Research Lectureship in Biomedical Science (1999), Academia Sinica, Taiwan
- ◆ Academic Award in Medical Science (1997), Ministry of Education
- ◆ Science and Technology Award (1992), Executive Yuan, Taiwan
- ◆ SCBA (Society of Chinese Bioscientists in America) Hepatitis Research Award, 1992
- ◆ Outstanding Research Award; National Science Council, 1990–1996
- ◆ Academician, Academia Sinica, since 2006
- ◆ National Chair-Professor of Medicine, Ministry of Education, 2006–2009
- ◆ TWAS member, 2011
- ◆ Member, IAC Advisory Board (International Advisory Committee International Symposium on Viral Hepatitis and Liver Disease) 2013

Specialty:

Hepatology, Gastroenterology, Internal Medicine, Molecular Virology, Cancer Research

Publications:

More than 580 original articles were published.

S8-2

Oncolytic Virotherapy for HCC

Pei-Jer Chen

Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan

For advanced HCC, molecular target therapy is the standard of care but other new treatment, such as SIRT, is in the development to rescue non-responsive patients. Tumor-specific lysis by engineered viral vectors has been explored, from p53 restoring to vaccinia or adenovirus vectors. A few early phase clinical trials were finished or ongoing, and generated interesting experiences. The telomerase-specific replication-competent oncolytic adenovirus, Telomelysin, was developed for virus-mediated preferential lysis of tumor cells. Its selectivity is derived from a human telomerase reverse transcriptase (hTERT) promoter-driven active viral replication, which occurs in cancer cells with high telomerase activity but not in normal cells lacking such activity. The oncolytic effect of Telomelysin has been investigated both in vitro using cell culture and in vivo using an immunocompetent in situ orthotopic HCC model. In this model, HCC developed spontaneously in the liver of HBx transgenic mice, which is pathologically and genetically similar to human HCC. In cell culture assay, Telomelysin lyses HCC cell lines at a low multiplicity of infection (MOI), ranging 0.77–6.35 (MOI [PFU/cell]). In the orthotopic HCC model, Telomelysin showed a potent oncolytic effect on HCC but spared normal liver tissue. Dose escalation analysis identified a safety dose of 1.25×10^8 PFU for this model. The effect of multiple injections of Telomelysin was also evaluated in this immunocompetent HCC model. It was found that the virus replicates in HCC after a second intratumoral injection despite an immune response induced by the previous injection. This preclinical study shows that Telomelysin and other oncoviruses can be used for treatment of human HCC at an appropriate dosage and that its tumor-killing activity persists after multiple injections. Clinical trials are warranted in the future.

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Speaker's Curriculum Vitae

Name Peter Schirmacher
Position Director
Institution Institute of Pathology, University
Hospital Heidelberg, Heidelberg,
Germany



Peter Schirmacher is the Director of the Institute of Pathology of Heidelberg University since 2004, coordinator of the SFB/TRR77 'Liver Cancer', funded by the German Research Foundation, and principal investigator of the German 'Virtual Liver' Network and several German consortial Health Research Networks (DKTK, DZL, DZIF). He is also founder and coordinator of the Tissue Bank of the National Center for Tumour Diseases (NCT), the comprehensive BioMaterialBank Heidelberg (BMBH) and the central Biobanking structures of DKTK and DZIF and has long-term experience in translational clinical studies. He is co-founder of the Liver Cancer Center Heidelberg (LCCH). Peter Schirmacher studied Medicine at Mainz University (graduation 1987, MD degree 1987) and Molecular Biology at Albert Einstein College, New York.

Professor Schirmacher is Chairman of the German Society of Pathology (since 2012) and Board member of the International Liver Cancer Association (ILCA) (since 2013), the German Telematic Platform (TMF) (since 2014) and the German Liver Foundation.

His research interests center on Molecular Tumor Pathology, especially of the liver, the Pathology of chronic liver diseases, the translation of these research findings into molecular diagnostics and associated technologies such as biobanking and virtual microscopy. He has published over 480 research papers and has participated in numerous diagnostic and therapeutic trials, preclinical research studies and clinical guidelines.

S8-3

Personalized Treatment in HCC: Umbrella Concept Combining Predictive Diagnostics, Clinical Trials and Evidence-Based Treatment

Peter Schirmacher

Institute of Pathology, University Hospital Heidelberg, Heidelberg,
Germany

Despite the fact that molecular analyses and functional studies in relevant model systems have provided a significant number of potential therapeutic options, hepatocellular carcinoma (HCC) has not benefited from the enormous progress in personalized cancer medicine when compared to other tumor entities. Specific reasons are the (A) lack of tumor-biomarker based clinical trials linked to the absence of consistent tumor biopsy based diagnosis (Torbensohn & Schirmacher, 2015), (B) significant deficiencies in trial design (Llovet, 2014) and (C) lack of local translational structures to promote efficient integration of personalized medicine for Liver Cancer.

Efficient local umbrella structures, as exemplified first by the Liver Cancer Center Heidelberg (LCCH), combine several clinical, diagnostic, and translational measures, including A) biomarker development and molecular testing programs supporting preclinical, trial associated, and translational diagnostic aspects, B) interdisciplinary tumor boards and SOPs combining clinical service with clinical trial issues, C) comprehensive patient databases linked to respective recall strategies D) active trial portfolio covering different therapeutic strategies E) off-label diagnostic and molecular tumor board approaches for rare tumor subentities and experimental targets F) efficient outreach/network structures to e.g. optimize trial recruitment and G) bedside-bench research strategies to pick up and solve defined questions arising from molecular diagnostics and related treatment. These structures may significantly benefit from integration in or association to Comprehensive Cancer Centers.

In conclusion, efficient local umbrella structures bridge the gap between standard treatment and clinical trials, promote personalized medicine, and are necessary measures to lower the distance in regard to personalized cancer treatment between liver cancer and other tumor diseases. Especially, patient management, trial recruitment, and translational research enormously benefit from these activities.

Speaker's Curriculum Vitae

Name Chiun Hsu, MD, PhD
Position Associate Professor
Institution Graduate Institute of Oncology,
National Taiwan University College
of Medicine, Taipei, Taiwan



Research Interest: New drug development for hepatobiliary cancers.

S8-4

Immunotherapy for HCC

Chiun Hsu

Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan

Immunotherapy represents a major breakthrough of systemic anti-cancer therapy for multiple cancer types. Patients with hepatocellular carcinoma (HCC) were usually excluded from early-phase trials of immunotherapy because most patients had underlying chronic viral hepatitis, and immune-related liver toxicity has been observed in previous studies of immunotherapy. However, preliminary results from early-phase clinical trials and translational studies suggested that checkpoint inhibitors may have promising anti-tumor efficacy in HCC. In this presentation the rationale of using immunotherapy for HCC will be summarized. Prospects of clinical trials of immunotherapy for HCC, alone or in combination with other systemic therapy, will be discussed.

Speaker's Curriculum Vitae

Name Winnie Yeo, MD FRCP
Position Professor
Institution Department of Clinical Oncology
Chinese University of Hong Kong



Professor Winnie Yeo is currently a clinical professor of the Department of Clinical Oncology, Faculty of Medicine, the Chinese University of Hong Kong. Professor Yeo graduated from King's College Hospital, University of London. She has undergone postgraduate training in Addenbrooke's Hospital, Cambridge, and at King's College, Westminster and Royal Marsden Hospitals in London before returning to Hong Kong. Professor Yeo has been the Chairman of the Medical Oncology Specialty of the Hong Kong College of Physicians between 2007 and 2013. She serves as a member and advisor in various expert panels and committees within the University, the Hong Kong Hospital Authority and various health advisory panels. She has authored and coauthored over 180 papers and her main research interests are management of liver, breast and gastric cancer patients as well as hepatitis B virus-related complications in cancer patients.

Research Interests: Management of liver, breast and gastric cancer patients. Hepatitis B virus-related complications in cancer patients.

S8-5

Systemic Chemotherapy for HCC

Winnie Yeo

Department of Clinical Oncology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, NT, Hong Kong, China

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related morbidity and mortality worldwide. To date, only surgical resection, local ablative therapies and liver transplantation offer chance of cure. However, in many parts of the world, only a proportion of patients presents with early stage HCC and are suitable for these approaches. For a considerable proportion of HCC patients, they either present with advanced stage disease, or have eventually failed despite locoregional treatments. For these patients, only systemic treatment can be considered with a palliative intent. To date, the only systemic agent that has been shown to provide survival benefit over best supportive care is the multikinase inhibitor of VEGFR, PDGFR and Raf, sorafenib. However, the overall prognosis of HCC patients remains poor. There is thus a need to improve therapeutic strategies for these patients with advanced disease.

In earlier studies, systemic cytotoxic chemotherapy had been widely tested in patients with advanced HCC. Unfortunately, these trials were usually small scaled studies mainly in single arm phase II setting. Doxorubicin, whether in combination to other agents or as a single treatment, is the most common cytotoxic agent evaluated in HCC. Doxorubicin has shown response rates of 10–20% in clinical trials. However, apart from one early randomized study which showed some survival advantage in patients treated with doxorubicin, there had been no other studies to confirm such finding. The demonstrated benefit was outweighed by the chemotherapy-related toxicities. In a significant proportion of HCC patients, the disease is associated with chronic hepatitis B or C virus infections; as such the tolerability to chemotherapy may be compromised by the concomitant chronic liver diseases. Supportive therapies, especially with regards to anti-viral therapies were suboptimal until the last decade.

In this talk, discussion will be made on historical data as well as the more recent large-scale phase III trials that assessed the role of cytotoxic chemotherapy. The efficacy combination therapy using cytotoxics with novel targeted agents will be discussed.

Speaker's Curriculum Vitae

Name Ann-Lii Cheng
Position Professor and Department Chair
Institution National Taiwan University
Hospital, Taipei, Taiwan



Ann-Lii Cheng is Professor and Chairman of the Department of Oncology of the National Taiwan University Hospital in Taipei, Taiwan. He received his MD degree, PhD degree, and his specialty training in Medical Oncology at the Medical School of the National Taiwan University. In 1990, he was a research fellow at the Comprehensive Cancer Center of the University of Wisconsin, Madison, USA. Dr. Cheng has been actively involved in basic and translational research in hepatocellular carcinoma and has published more than 200 peer-reviewed articles. He received the 'Outstanding Research Award' from the National Science Council of Taiwan, and the 'Outstanding Cancer Research Award' from the Chinese Oncology Society. He became 'Distinguished Professor' of National Taiwan University in 2006, and was elected as Fellow of American Association for the Advancement of Science (AAAS) in 2007. Dr. Cheng is an active member of the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO). He has served on the editorial boards of *Oncology (Basel)*, *Asia-Pacific Journal of Clinical Oncology*, and *Targeted Oncology – Biotherapies for the Clinicians in Oncology*. In addition, Dr. Cheng is Chairman of the Chemotherapy Committee of the Taiwan Cooperative Oncology Group, of which he was one of the founding members. He received the national award of 'outstanding contributions for science and technology' in 2008, and a national award for academic excellence in 2010. He served as president of the Taiwan Oncology Society during 2009–2011. He was elected as National Professorship Taiwan 2013.

Research Interest: Translational research for endemic cancers of Asia-Pacific region

S8-6

Retrospective Pooled Analysis of Advanced HCC Patients in SHARP and AP Randomized Clinical Trials

Ann-Li Cheng¹, Josep M. Llovet², Gerold Meinhardt³,
Keiko Nakajima³, Yoriko DeSanctis³, Jordi Bruix⁴¹Department of Oncology, National Taiwan University Hospital, Taiwan,²Liver Cancer Program, Hofstra-North Shore-LIJ School of Medicine, Lenox Hill Hospital, ³Bayer HealthCare Pharmaceuticals, ⁴BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Spain

Background: Surveys of current practice patterns for HCC indicate that sorafenib (SOR) treatment (TRT) is initiated late after extensive use of loco-regional TRTs. Reports of prognostic factors for overall survival (OS) and predictive factors for TRT effect of SOR are often based on retrospective analyses with no control arm. Despite evidence from phase 3 randomized clinical trials (RCTs), TRT practices are mostly based on empirical experience. To evaluate predictive factors, we performed an exploratory pooled analysis of patients (pts) with advanced HCC randomized into the SOR phase 3 trials, SHARP (n = 602) and Asia-Pacific (AP; n = 226).

Methods: Both SHARP and AP trials showed a significant OS benefit of SOR over placebo (PBO). To identify prognostic factors for OS, exploratory univariate (UV) and multivariate (MV) analyses were performed using the Cox proportional hazard regression model. Both tumor and non-tumor related baseline variables were assessed (see table). Hazard ratios (HR) and median OS were evaluated across the pooled subgroups in a similar manner. To assess consistency of SOR benefit, the interaction term between TRT and each subgroup was evaluated using Cox proportional hazard model. This exploratory analysis should be interpreted cautiously as it may be influenced by small sample size and low event count. No adjustment was performed for multiplicity.

Results: 827 pts (448 SOR; 379 PBO) were included. At baseline AP compared to SHARP pts had more advanced disease, a higher prevalence of EHS, ECOG PS 1-2, and a lower percentage of HCV (12% vs. 73%) vs. HBV (30% vs. 8%). Prognostic factors for OS were BCLC stage, Child-Pugh score, tumor burden, tumor size, ECOG PS, bilirubin and albumin in both arms. A SOR benefit for OS compared with PBO was consistently observed across all subgroups, with numerically lower HRs observed for pts without EHS, tumor burden, and HCV. A TRT by subgroup interaction was observed at the 10% significance level for EHS, tumor burden and number of target lesions at baseline, and HCV. These interactions had similar direction in treatment effect.

Conclusions: The SOR benefit was generally consistent irrespective of prognostic factors for survival, suggesting all subgroups evaluated had benefit from SOR over PBO. These data also suggest a potentially greater magnitude of benefit for SOR in some subgroups of pts.

Table 1. Univariate OS pooled analysis^a with major prognostic factors

Baseline covariates	N (PBO; SOK*)	Events	Median OS (mos)		HR (SOR/PBO)	Treatment interaction p-value ^b	Baseline covariates	N (PBO; SOK*)	Events	Median OS (mos)		HR (SOR/PBO)	Treatment interaction p-value ^b
			PBO	SOR	[95% CI]					PBO	SOR	[95% CI]	
Tumor related variables							Hepatitis B						
ECOG PS							No	540 (266; 674)	349	7.4	9.9	0.69 [0.55–0.85]	0.516
0	373 (183; 190)	224	9.8	13.0	0.71 [0.54–0.92]	0.465	Yes	236 (90; 146)	172	4.8	6.5	0.78 [0.57–1.06]	(Yes vs No)
1 and 2	454 (196; 258)	323	4.8	7.4	0.67 [0.54–0.84]		Hepatitis C						
BCLC stage							No	568 (265; 303)	398	6.5	7.6	0.81 [0.66–0.99]	0.035
Stage B	113 (55; 58)	58	13.4	15.1	0.78 [0.46–1.32]	0.431	Yes	199 (88; 111)	120	7.9	14.0	0.47 [0.32–0.69]	(Yes vs No)
Stage C	714 (124; 390)	489	6.0	8.5	0.69 [0.57–0.82]		Alcohol Use						
Tumor burden							No	636 (287; 349)	419	6.5	9.4	0.67 [0.55–0.81]	0.361
Absent	229 (107; 122)	112	10.6	15.7	0.53 [0.37–0.78]	0.081	Yes	191 (92; 99)	128	8.5	9.5	0.82 [0.58–1.17]	(Yes vs No)
Present	598 (272; 126)	435	5.6	7.3	0.77 [0.64–0.93]	(Present vs Absent)	Non-tumor related variables						
MVI							Albumin (median = 1.96 g/dl)						
No	515 (210; 285)	294	10.0	12.7	0.70 [0.56–0.88]	0.947	≤median	355 (143; 212)	277	4.1	6.6	0.64 [0.50–0.82]	0.943
Yes	310 (148; 162)	252	4.5	6.0	0.69 [0.53–0.89]	(Yes vs No)	>median	472 (236; 236)	270	9.8	13.6	0.61 [0.49–0.80]	(>median vs ≤median)
EHS							Total bilirubin (median = 0.77 mg/dl)						
No	365 (178; 187)	218	7.2	13.8	0.55 [0.42–0.72]	0.015	≤median	473 (214; 259)	287	9.2	10.7	0.70 [0.56–0.89]	0.934
Yes	462 (201; 261)	329	7.0	7.3	0.84 [0.67–1.05]	(Yes vs No)	>median	354 (165; 189)	260	4.9	6.7	0.72 [0.56–0.93]	(>median vs ≤median)
MVI without EHS							Race						
No	689 (307; 382)	440	8.5	9.5	0.74 [0.62–0.90]	0.283	Asian	274 (100; 174)	203	4.8	6.7	0.78 [0.59–1.04]	0.3664
Yes	136 (71; 65)	106	4.5	6.8	0.53 [0.35–0.80]	(Yes vs No)	Non-Asian	553 (279; 274)	344	7.9	11.4	0.67 [0.54–0.82]	(Non-Asian vs Asian)
Number of target lesions													
1	208 (99; 109)	130	7.0	8.8	0.73 [0.51–1.05]	0.078							
2	165 (79; 86)	99	9.3	11.8	0.59 [0.40–0.89]	(0, 1, 2, 3, >3)							
3	147 (70; 77)	91	5.5	11.5	0.49 [0.32–0.75]								
>3	195 (136; 165)	218	6.4	7.3	0.85 [0.65–1.12]								

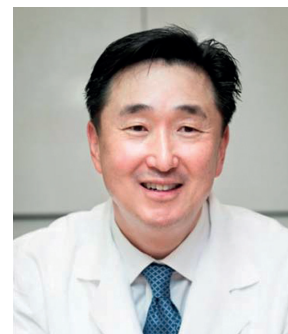
*SOR group one subject with BCLC stage D was excluded. ^aITT population; ^bWald test for individual effects (p-value).

Session 9

APPLE Consensus Workshop: Searching Consensus for Controversies

Speaker's Curriculum Vitae

Name Kyung-Suk Suh
Position Professor and Chairman
Institution Department of Surgery Seoul
National University College of
Medicine



Professor Suh graduated Seoul National University Medical College in 1984. After finishing residency and fellowship at the Department of Surgery, Seoul National University Hospital, he joined same Department as a Faculty staff. He is currently a Professor and Chairman at the Department of Surgery, Seoul National University College of Medicine. He is now chairman of the Korean Liver Cancer Study Group and President of the Korean Association of Hepato-biliary-pancreas Surgery. He has main interest in liver surgery including liver transplantation. As a pioneer in the field of liver transplantation, he developed many new techniques and published many clinical papers. Now, he is a principal investigator in several nation-wide multi-center studies associated with liver transplantation and surgical treatment of HCC.

Research Interest:

Prognostic factor and tumor marker for HCC
HCC pathogenesis in the fatty liver
Liver transplantation for the advanced HCC
New technique in living donor liver transplantation

S9-1

Transplantation for Child-Pugh A/B in Asia

Kyung-Suk Suh

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Living donor liver transplant (LDLT) became one of the important treatment modalities for hepatocellular carcinoma (HCC) in Asian countries. LDLT for HCC has been increasing and it has recently accounted for about 50% of adult LDLT in SNUH). The classical indication of LT for HCC in Asian countries is early staged HCC with poor liver function. For resectable cases with good liver function, resection instead of primary LDLT is considered first in most Asian countries. The Milan or UCSF criteria were still used as a selection criteria even in LDLT. However, its indication has been expanded in LDLT because a living graft is dedicated to only one recipient. Nowadays, the indication of LDLT for HCC has expanded selectively and experience in advanced stage and/or good liver function has accumulated in our center.

In Korea, HCC is most commonly associated with HBV. HBV can be cured by LT. Therefore, LDLT which could be used in the treatment both of the tumor and background liver seems to be a rational approach for early staged patients regardless of liver function. However, there are several limitations of LDLT for HCC such as risk to a live donor, high cost and lifelong immunosuppression. Therefore, primary LDLT for resectable early HCC has been under some debate. Similar with other studies, even though LT showed a lower incidence of tumor recurrence compared with resection in patients with early HCC, the survival rate was similar between the two treatment modalities in our analysis (1). Therefore, primary resection and salvage LT after recurrence has been considered as the gold standard. However, recurrence occurred after resection for early staged HCC in half of patients within 3 years and some patients showed non-transplantable recurrence ranging from 20 to 75% according to the previous studies. Recently, some patients with early staged HCC insist on LDLT as a primary treatment because of the high recurrence risk and potential non-transplantable recurrence after other treatment including resection. Because there have been no clear criteria to predict no-recurrence or transplantable-recurrence after primary resection, the physician could not strongly refuse this request. We recommend primary resection first in most cases. However, we selectively accept primary LDLT in cases with early HCC with good liver function, especially in the following situations: 1) relatively young patients with strong family support, or 2) high chance of recurrence after resection, e.g. multiple dysplastic nodules in the background liver. The proportion of Child A patients in LDLT patients for HCC was increasing up to around 10–20% in our center.

However, when we compared primary liver transplantation and resection in cases with early staged HCC with poor tumor characteristics (high AFP, micro-vascular invasion or high tumor grade), the survival of LDLT was inferior to that of resection. Therefore, the recommendation of primary or pre-emptive LT in early HCC with poor tumor characteristics because of high chance of non-transplantable recurrence can't always be justified in LDLT situation.

Speaker's Curriculum Vitae

Name Kwang-Hyub Han, MD
Position and Institution Professor and Chairman,
Department of Internal Medicine,
Director, Liver Center, Severance
Hospital



Kwang-Hyub Han, MD, is professor and chairman of Department of Internal Medicine, and staff gastroenterologist (hepatologist) at Yonsei University College of Medicine, and chief of Liver Center, Severance Hospital, Seoul, Korea. He was the director and principal investigator of a 9-year project, 'Clinical Research Center for Liver Cirrhosis,' granted from the Ministry of Health and Welfare and Health Technology Planning and Evaluation Board. He organized the 1st Asian-Pacific Primary Liver Cancer Expert (APPLE) meeting as a co-chairman and He was a governing board member of the International Liver Cancer Association and the president of Korea Liver Cancer Study. He served as a committee member of the working party for the Asian-Pacific consensus statement on hepatocellular carcinoma guidelines 2008.

At present, he is now the president of APPLE association and the Korean Association for the Study of the Liver. He is also serving as an editorial board member for *Journal of Hepatology*, and assistant editor of *Hepatology International*. He is the author of several book chapters on topics such as hepatocellular carcinoma, hepatitis B and C viruses, and liver disease, as well as more than 300 articles published in national and international journals on similar topics, in addition to that of liver fibrosis, cirrhosis, and treatment of hepatocellular carcinoma, among others.

S9-2

Sub-Classification of Intermediate Stage HCC and Treatment Strategy

Kwang-Hyub Han

Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Republic of Korea

The BCLC staging system has been widely used in clinical practice to help physicians determine the best treatment option at each disease stage. Proper identification and treatment of intermediate-stage HCC, which is the largest group, is crucial for optimizing outcomes. However, the intermediate stage of HCC comprises a population with highly heterogeneous clinical characteristics. These patients have large/multifocal HCC (defined as more than three tumors regardless of size, two to three tumors >3 cm in maximal diameter, or one single unresectable tumor >5 cm) and Child-Pugh class A and B liver function in the absence of cancer-related symptoms, macrovascular invasion, or extrahepatic spread. The current guidelines recommend TACE as a first-line treatment for intermediate-stage patients (BCLC-B). However, not all patients are optimal candidates who may benefit from TACE and require other treatment modality. Furthermore, repeated TACE may be needed due to incomplete treatment after TACE.

However, no subgroup stratification has been suggested for this population in the current BCLC staging system, which might pose a challenge to the development of tailored treatment strategies. Recently, Bolondi et al. proposed sub-classification of BCLC stage B HCC into four stages (B1–B4). It also included liver transplant patients beyond the Milan criteria but within up-to-seven criteria. In the similar context, curative treatments, including liver resection or liver transplantation, have been applied to a selected group of patients with BCLC stage B HCC considering performance status, liver function, tumor size, tumor number, and the location of tumors and they have achieved a good clinical outcome. The other group also reported that selection scoring system to identify suitable candidates were necessary. In Korean study, we analyzed long-term outcome of patients with BCLC stage B HCC. Based on tumor size, number and Child class, the clinical outcomes are quite diverse. Therefore, sub-classification of intermediate stage will be necessary to achieve the maximal treatment response. Since an appropriate combination strategy based on baseline patient and tumor characteristics may increase the survival of patients with intermediate stage HCC, sub-classification should be approached to find the optimal candidate for treatment modalities.

Satellite 1

Basics, Genomics, Molecular Biology and Therapy

Speaker's Curriculum Vitae

Name	Peter R. Galle, MD, PhD
Position	Chairman
Institution	First Department of Internal Medicine, University Medical Center, Mainz



Dr. Galle majored in internal medicine at the Universities of Berlin and Marburg/Germany, Hammersmith Hospital, London/UK and University of Texas/USA and received his M.D. degree from Marburg University and Ph.D. degree from Heidelberg University.

Initially he held a position as postdoctoral fellow in Molecular Biology at the Centre for Molecular Biology Heidelberg working on the replication of hepatitis B viruses. Afterwards he completed his residency in Internal Medicine and Gastroenterology at the University Hospital of Heidelberg. In 1998 he became Director of the I. Medical Department in Mainz and from 2005–2008 he held the CEO position of Mainz University Hospital.

He is member of several national and international societies such as the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), served as Co-editor for the Journal of Hepatology and is on the Editorial Boards of several other Journals. He is member of the Executive Board and President of the International Liver Cancer Association (ILCA).

His research has focused on elucidating important aspects of apoptotic cell death in the liver, immune escape of tumour cells and on clinical and molecular aspects of hepatocellular carcinoma. He was awarded several prizes, amongst others the prestigious Tannhauser award, the highest prize of the German Society for Digestive Diseases. He has published more than 500 peer-reviewed papers.

Google Scholar Citation Report (April 2015)

Sum of the Times Cited: 36727

h-index: 89

Satellite1-1

Role of Macrophages in HCC

Peter R. Galle

University Medical Center, Mainz, Germany

Tumor-associated macrophages (TAM) found in the environment of hepatocellular carcinomas (HCC) are associated with unfavorable prognosis. Macrophages are classically categorized in polarized macrophages (M1) involved in (pro-) inflammatory responses and in alternatively polarized macrophages (M2) involved in tissue repair.

TAMs typically show an M2-polarization and, thus, are able to provide tissue repair signals such as growth factors, including endothelial growth factor (EGF), vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF). With this repertoire TAMs can promote cell proliferation and neo-angiogenesis and in the end support tumor progression.

Sorafenib is a multi-kinase inhibitor and currently the only approved systemic treatment option in advanced HCC. Here we analyze the effect of sorafenib on macrophage polarization and function.

We are able to demonstrate that sorafenib shows 'off target' effects on macrophages. As a result of sorafenib treatment of macrophages *in vitro* a change macrophage polarization towards M1 is observed. This results in an activation of NK effector function via macrophages. Overall, sorafenib treatment results in reduced growth factor expression and activity of polarized macrophages.

In conclusion, modulation of macrophage function and activity might contribute to the anti-cancer effect of sorafenib.

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Speaker's Curriculum Vitae

Name Daeghon Kim, MD, PhD
Position Professor and Principal Investigator
Institution Dept. of Gastroenterology and Hepatology, Chonbuk National University Medical School and Hospital, Republic of Korea



Daeghon Kim studied Medicine at Chonbuk National University Medical School and graduated in 1979. Following this, he completed a clinical fellowship in Chonbuk National University Hospital followed by a research fellowship at the Whitehead Institute affiliated with MIT in USA and Chonbuk National University Graduate School of Medicine, where he received his PhD degree in Medical Science in 1987. Professor Kim is currently a Professor at the Department of Gastroenterology and Hepatology, Chonbuk National University Medical School since 1986. He was a Dean of Chonbuk National University Medical School (2010–2012).

Professor Kim is the recipient of numerous awards including the Kim Jinbok Cancer Award in Korean Foundation of Cancer Research (2013), Liver Cancer Society for Academic Award in the Korean Liver Cancer Study Group (2010) and Top 100 of Excellent R&D Results in Ministry of Education, Science and Technology (2010). He has published many International scientific peer review papers in well-regarded journals in addition to domestic scientific papers.

His research interest is 'Molecular pathogenesis and signal transduction pathway in hepatocarcinogenesis and molecular targets of HCC diagnosis and treatment'.

Satellite1-2

Ribosomal Association Factor NACA Is a Molecular Adaptor for ERK Activation and Mitotic Progression in Tumor Cells

Mijin Lee, Minjeong Kim, Jonghyun Kim, Goungran Yu, Daeghon Kim

Department of Gastroenterology and Hepatology, Chonbuk National University Medical School and Hospital, Jeonju, Republic of Korea

The alpha-chain of the nascent-polypeptide-associated complex (NACA) is up-regulated in various human tumors. The aim of this study was to investigate the molecular implications and biological significance of NACA in hepatocellular carcinoma (HCC).

NACA expression was initially evaluated using public gene expression data of HCC as well as HCC tissues and cells. Using short hairpin RNA (shRNA)-mediated knockdown, the molecular mechanism of NACA in tumor cell growth was assessed in experimental cell culture and *in vivo* animal models.

NACA is highly expressed in HCC tissues and cells. Knockdown of NACA results in decreased tumor cell proliferation, which was found to be related to inhibition of extracellular signal-regulated kinase 1 and 2 (ERK1/2) phosphorylation. Furthermore, silencing NACA or down-regulation ERK1/2 expression reduced levels of G₂/M-phase cyclins (cyclin A and cyclin B1) and their associated kinases (Cdc2 and Cdc25C). However, knockdown of the beta-chain of the nascent-polypeptide-associated complex (NACB) did not alter the activity of these signaling molecules. NACA was found to bind to ERK1/2 and appeared to function as an adapter to accelerate its activation, which in turn enhances mitotic progression of tumor cells.

In conclusion, our results suggest that up-regulation of NACA is critical for mitotic cell growth of HCC cells. Therefore, NACA may be a useful target molecule for HCC therapy.

Speaker's Curriculum Vitae

Name Shuang-Jian Qiu, MD, PhD
Position Professor
Institution Department of Liver Surgical
Oncology, Liver Cancer Institute,
Fudan University, Shanghai, China



Professor of Liver Surgical Oncology, Liver Cancer Institute, Fudan University. He received his medical education at Fudan University (formerly Shanghai Medical University) in Shanghai, China, where he got his M.D. and Ph.D. degree successively. He worked as a Visiting Research Scientist at the University of Pittsburgh Transplantation Institute from August 1999 to December 2000.

Professor Qiu is focusing on the study of microenvironment of hepatocellular carcinoma (HCC), especially the role of immune cells in the progression of HCC. He has published over 30 papers in the peer-reviewed English journals including J Clin Oncol, J Hepatol, Clin Cancer Res, etc. He is the member and secretary of Liver Cancer Group, Chinese Society of Hepatology, the vice director of Cross-Strait Exchange Association of Liver Cancer, the member and secretary of the Shanghai Society of Hepatology, a member of Chinese Society of Liver Cancer, Chinese Anti-Cancer Association, a member of Cancer Immunology Subcommittee of Shanghai Society for Immunology. He received several national and local awards and grants.

Research Interest: Hepatology, Microenvironment of HCC.

Satellite1-3

Local Immune Microenvironment and Therapeutic Strategies for Human Hepatocellular Carcinoma

Shuang-Jian Qiu, Yong Yi, Jia Fan

Liver Cancer Institute, Zhongshan Hospital and Fudan University, Shanghai, China

Hepatocellular carcinoma (HCC), the third leading cause of cancer-related death worldwide, is a disease of microenvironment and immunity. Accumulating evidence has demonstrated that tumor microenvironment plays an important role in the development or progression of this lethal disease. It is now clear that the local immune system plays a dual role in HCC: It can not only suppress tumor formation and outgrowth but also promote tumor progression either by selecting for tumor cells more fit to survival in immunocompetent host or by establishing conditions within the tumor milieu that facilitate tumor outgrowth. The balance between anti-tumor and pro-tumor factors located in the tumor microenvironment is important for patient outcome, a balance toward pro-tumor factors indicated weak anti-tumor activities and poor outcome and vice versa. Multiple mechanisms underline the tumor evasion from immune surveillance was demonstrated including loss of tumor antigen, establishment of an immunosuppressive state within the tumor microenvironment by recruiting suppressive cells regulatory T cells (Treg cells) and myeloid-derived suppressive cells (MDSC); by secreting suppressive cytokines IL-10 and TGF- β ; by expressing the negative co-stimulatory molecules CTLA-4, PD-1, PD-L1 and B7-H3; and by consuming IL-2, a cytokine that is essential for maintaining cytotoxic T lymphocyte function. The immunotherapeutic strategy based on overcoming barriers within the microenvironment, briefly by enhancing anti-tumor power in combination with attenuating pro-tumor strength, was widely accepted. Until now, several immunotherapeutic studies demonstrating promising results in HCC. These strategies include intratumoral injection of an oncolytic virus expression granulocyte macrophage colony stimulating factor, DC vaccine treatment, adoptive transfer of cytotoxic T lymphocytes, anti-CTLA-4 treatment, interferon- α therapy, and immunity regulator-thymosin. Although clinical benefits may be accessible in some of these approaches as single agents, there is a clear opportunity in HCC to evaluate these in combination with the standard modalities such as transhepatic arterial chemotherapy and embolization, radiofrequency ablation, and radiotherapy to more effectively harness the immune response. Moreover, immunotherapeutic treatment after hepatectomy may improve patient outcome by effectively killing residual cancer cells or tiny lesion of recurrence.

Speaker's Curriculum Vitae

Name Bruno Sangro, MD, PhD
Position Director
Institution Liver Unit, Clinica Universidad de Navarra, Pamplona, Spain



Prof. B. Sangro is Director of the Liver Unit at Clinica Universidad de Navarra, Aggregate Professor of Medicine at the University of Navarra School of Medicine, Head of the Area of Digestive and Metabolic Diseases at the Navarra Institute for Research (IDISNA) and Head of the group for Translational Research in Hepatology in the National Biomedical Research Network Center for Liver and Digestive Diseases (CIBERehd). He is also advisor for the Spanish and the European Agency for Medicinal Products. His basic and clinical research has mainly focused on liver cancer, with a high priority on therapeutic innovation. The Liver Unit of Clinica Universidad de Navarra has pioneered several approaches to the treatment of liver cancer from expanded criteria for liver transplantation to locoregional vascular therapy including intraarterial infusion chemotherapy, transarterial embolization and radioembolization, and systemic advanced therapies including gene therapy or immunotherapy.

Satellite1-4

Targeting the Immune System for the Treatment of HCC

Bruno Sangro

Liver Unit, Clínica Universidad de Navarra, IDISNA, CIBEREHD, Pamplona, Spain

The immune system plays an important role in the outcome and response to treatment among patients with hepatocellular carcinoma (HCC). The importance of HCC antigenicity is illustrated by the reduction in post-surgical tumor recurrence when dense lymphocytic tumor infiltration is present or by the association of T-cell responses against tumor antigens and patient survival. Tumor growth despite immune recognition indicates the superior activation of wound-healing over immune rejection in the inflammatory processes occurring in the tumor microenvironment, where effector T cells are amalgamated with other stromal cells that have immunosuppressive, cytoprotective, stromagenic and pro-angiogenic properties. In this environment, continued exposure to tumor antigens leads to T cell exhaustion, favored by intratumor expression of immune check-point inhibitors. Cell-based immunotherapy including adoptive cell therapy with cytokine-induced killer cells (CIK) or dendritic cell vaccination has shown a favorable safety profile but weak clinical activity. In the very recent years we are witnessing the dawn of a new era in immunotherapy of HCC with different approaches. Peptides derived from tumor-associated antigens identified by genome-wide analysis of specific mutations may be used for cancer vaccination. The local production of immunostimulating cytokines after intratumoral gene transfer using defective or oncolytic viruses has produced stimulating clinical results that need further verification. And monoclonal antibodies that modulate the activity of immune check-point molecules that are critical determinants of tumor evasion to immunity have revolutionized the field of cancer immunotherapy and will probably do so with HCC too. Promising activity has been reported for tremelimumab, a CTLA-4 inhibitor, and a clinical trial testing the PD-1 antibody Nivolumab is underway. Future progress will probably come from a better understanding of the mechanisms of cancer-related immunosuppression, improvement in agents and strategies, and combination of the available therapeutic tools.

Speaker's Curriculum Vitae

Name Naoshi Nishida, MD, PhD
Position Associate Professor
Institution Department of Gastroenterology
and Hepatology, Kinki University
Faculty of Medicine, Osaka, Japan



Professional Experience:

2011-present Associate Professor, Department of Gastroenterology and Hepatology, Kinki University, Faculty of Medicine, Osaka, Japan
2007–2011 Lecturer, Department of Gastroenterology and Hepatology, Kyoto University, Graduate School of Medicine, Kyoto, Japan
2006–2007 Assistant Professor, Department of Gastroenterology and Hepatology, Kyoto University, Graduate School of Medicine, Kyoto, Japan
2004–2006 Research fellow, Division of Gastroenterology. Department of Internal Medicine, Baylor University Medical Centre, Dallas, TX
1997–2004 Assistant Professor, Department of Medicine and Clinical Science, Kyoto University, Graduate School of Medicine, Kyoto, Japan
1996–1997 Instructor, Research Institute for Production Development, Kyoto, Japan
1993 Ph.D. Kyoto University Graduate School of Medicine, Kyoto, Japan
1985 M.D. Osaka Medical School, Osaka, Japan

Honors and Awards:

2009 Investigator Award of 45th Annual Meeting of Japan Society of Hepatology
2008 Kanmuri Award of the Japan Society of Hepatology
1993 Investigator Award of the Japan Society of Hepatology

Satellite1-5

Epigenetics in HCC Pathogenesis

Naoshi Nishida, Masatoshi Kudo

Department of Gastroenterology and Hepatology, Kinki University Faculty of Medicine, Osaka, Japan

To know the role of DNA methylation in the promoter of tumor suppressor genes (TSGs) in HCC pathogenesis, we have analyzed a total of 482 liver tissues including 177 pairs of HCCs and matched non-tumor livers and 128 liver biopsies from chronic hepatitis C (CHC) patients for quantitative methylation analysis. After the selection of a subset of TSGs, which harbored distinctly high levels of methylation in early HCCs, Kaplan-Meier analyses were performed to determine time-to-HCC occurrence in CHC patients classified based on the methylation profiles. In the CHC patients, methylation frequencies in these TSGs were associated with shorter time-to-HCC occurrence ($p < 0.0001$), and number of methylated genes was an independent risk for HCC emergence (hazard ratio = 5.21, 95% CI = 2.25–11.76, $p = 0.0002$).

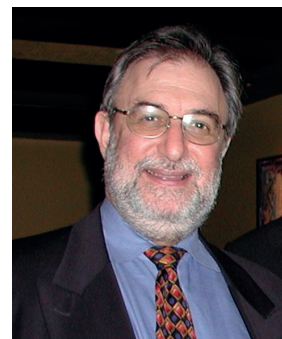
As persistent inflammation should trigger oxidative damage and contribute to the emergence of HCC, we next tried to clarify the association between oxidative DNA damage and epigenetic alterations using the 128 liver biopsy samples from CHC patients. The DNA oxidation and methylated TSG numbers were quantified using immunohistochemical analysis of 8-hydroxydeoxyguanosine (8-OHdG) and quantitative PCR (qPCR) for 11 TSGs, respectively. The analysis showed that the high level of 8-OHdG was the only variable that was significantly associated with the increased number of methylated TSGs ($p < 0.0001$). We also performed a chromatin immunoprecipitation-qPCR (ChIP-qPCR) assay using cell lines after the induction of 8-OHdG and alteration of active chromatin, repressive chromatin status and 8-OHdG levels after DNA oxidation were quantified. Thirty promoters of 25 different TSGs were examined; the ChIP-qPCR revealed that the 8-OHdG-bound promoters showed an alteration of chromatin modification from an active to a repressive form. These evidences suggest that the oxidative DNA damage could alter the chromatin status, which should lead to abnormal methylation of TSGs, and contributes to hepatocarcinogenesis.

Satellite 2

Surveillance and Diagnostic Algorithm

Speaker's Curriculum Vitae

Name Morris Sherman
Position Professor of Medicine
Institution University of Toronto, Toronto, Ont., Canada



Dr. Sherman studied medicine at the University of Witwatersrand in Johannesburg South Africa, where he graduated in 1972. After interning at Baragwanath Hospital in Soweto he moved to complete training in Internal Medicine and Gastroenterology at the University of Cape Town and Groote Schuur Hospital in Cape Town. He also completed a PhD in protein biochemistry at Groote Schuur in 1981.

In 1982 he undertook a post-doctoral fellowship at the Albert Einstein College of Medicine in New York. On completion of the fellowship he moved to Toronto, where he has been ever since, and is now Professor of Medicine.

Dr. Sherman has long had an interest in hepatocellular carcinoma, starting from internship. Baragrawath Hospital served a very large population of black South Africans, in whom hepatitis B and hepatocellular carcinoma was common. His PhD thesis in Cape Town included studies on the expression of Glutathione S-Transferases in hepatocellular carcinoma in man. In New York he studied the restriction enzyme maps of hepatitis B viral DNA integrated into human hepatocellular carcinoma.

In Toronto he continued his studies of hepatitis B and hepatic carcinogenesis. In the late 1990's he became interested in the early diagnosis of HCC, HCC screening strategies and characterization of lesions found in the liver during screening for hepatocellular carcinoma.

Dr. Sherman has previously been President of the Canadian Association for Study of the Liver, and is Chairman of the Board of the Canadian Liver Foundation. He has also worked as a consultant to federal and provincial governments in Canada, and to numerous pharmaceutical companies involved in the development of treatment for viral hepatitis and hepatocellular carcinoma.

He has participated in and co-authored several practice guidelines for hepatocellular carcinoma and viral hepatitis for national and international professional societies and has lectured around the world on these topics.

Satellite2-1

Assessment of HCC Risk

Morris Sherman

Professor of Medicine, University of Toronto, Toronto, Ont., Canada

There are two components to assessing the risk that an individual might have for developing hepatocellular carcinoma (HCC). The first is to assess the likelihood of developing HCC, and the second is to assess what threshold of risk makes it necessary to intervene, and what should that intervention be.

Assessment of Risk:

The method of developing a risk score involves initially retrospective analysis of a cohort of patients potentially at risk and identifying those factors that are associated with the development of HCC. This is performed by univariate analysis. Multivariate analysis is then used to determine which of the associated factors are independently associated with increased risk. The weights associated with each factor are used to calculate the risk score. This is then validated in a separate cohort. Other validation processes include comparing the predicted risk with the actual development of HCC. Finally external validation is required in similar and then different populations.

There are several systems available to assess the risk of developing HCC. Traditional risk factors include cirrhosis, age, and gender. These have been developed for different populations. The REACH-B score [1], the CU-HCC score [2] and the GAG HCC [3] score have been developed to assess the risk in patients with chronic hepatitis B. The CU-HCC score and the GAG HCC score include all patients with hepatitis B. The REACH B score excludes patients with known cirrhosis. The REACH-B score has been externally validated, but the others have not. However, the REACH-B score does not seem to accurately predict HCC development in Caucasian populations [4].

The ADRES-HCC score was developed in a population of patients awaiting liver to predict the development of HCC transplantation, and has not been validated in any other population [5]. Sharma et al have developed a predictive score in a population of patients with cirrhosis of various causes [6]. This is the only score in cirrhotics that takes etiology into account, and clearly shows that the risk differs by etiology, so that etiology should be a factor in assessing risk.

At least two groups in Taiwan have developed scores that are applicable to the general population [7, 8]. This may be appropriate in areas where HCC is very common, but is unlikely to be applicable in low incidence areas.

El Serag et al. [9] have developed a score taking advantage of the fact that false-positive AFP values are associated with active hepatic inflammation. Therefore an elevated AFP in the presence of elevated ALT is less likely to be associated with HCC than if the ALT was normal. Their retrospective analysis looked at patients with HCC and reviewed the ALT AFP and other measurements obtained 6 months before the diagnosis of HCC. They developed a scoring system using these measurements. This has the advantage of increasing the specificity of AFP measurements. This score has been validated internally, but not yet externally.

What level of risk warrants intervention?

Until recently the decision to intervene (essentially this means undertaking surveillance) was based on cost efficacy analyses. These suggested that if the incidence of HCC exceeded 1.5–2%/year surveillance was effective in reducing mortality and also was cost-effective. This incidence was exceeded by patients with cirrhosis from hepatitis B or hepatitis C and patients with Stage 4 primary biliary cirrhosis. A single analysis in hepatitis B suggested that if the incidence exceeded 0.2%/year surveillance was once again effective and cost effective. Thus the guidelines from the AASLD and EASL chose those cut-off's to recommend surveillance [10, 11]. More recently decision curve analysis has been used [8]. This suggests that if the risk of HCC exceeds 2% surveillance has a significant net benefit. This level of risk is achieved by untreated hepatitis B and hepatitis C cirrhosis, and possibly by cirrhosis due to NAFLD. This was in a population in Taiwan in which the incidence of HCC was high. This cut-off may not be the same in other populations.

What intervention

The intervention that is suggested by the identification of a sufficiently high risk is surveillance. How the surveillance should be conducted remains controversial, with use of biomarkers and more frequent surveillance being the norm in Asia, whereas in Europe and North America although some still use biomarkers these are not recommended by the AASLD guidelines and recommended only if ultrasound is not available in the EASL guidelines.

Comment

All of these risk scores have been developed in untreated populations. However, there is good evidence that successful treatment of hepatitis C and hepatitis B, even in cirrhotics reduces the incidence of HCC. Whether the reduction in incidence is enough to eliminate surveillance or at what stage that reduction in incidence is reached remain unknown. This limits the applicability of all the scores described above.

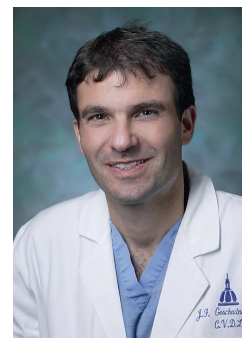
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Speaker's Curriculum Vitae

Name Jean-Francois H. Geschwind
Position Chairman
Institution Diagnostic Radiology and Imaging
Sciences at Yale University School
of Medicine, New Haven, CT, USA



Jeff Geschwind, MD, is the new Chairman of Diagnostic Radiology and Imaging Sciences at Yale University School of Medicine and Radiologist in Chief at Yale New Haven Hospital. He is also a Professor of Radiology, Surgery, and Oncology at Yale University in New Haven, Connecticut. Dr. Geschwind began his early medical training at the University of Paris School of Medicine and completed his medical degree at Boston University School of Medicine, Boston, MA. He completed his residency training in Diagnostic Radiology at the University of California at San Francisco and fellowship at Johns Hopkins where he remained on faculty for 19 years as the chief of vascular and interventional radiology.

Dr. Geschwind has focused his clinical expertise on treating hepatic cancer and other malignancies, and created the Center of Oncologic Interventions while he was at Johns Hopkins.

As lead or co-investigator on more than 50 clinical trials, Dr. Geschwind's research has been published in many top peer-reviewed journals, including the *Journal of Clinical Oncology*, *Radiology*, *Clinical Cancer Research*, *Cancer Research* and *Annals of Surgery*. He serves on the editorial board of *Anticancer Research*, *Cardiovascular and Interventional Radiology*, *Radiology*, and *Intervention Oncology Today* among others, and he is a consultant to the Editor of *Radiology*. In 2008, Cambridge University Press published Dr. Geschwind's book, *Interventional Oncology Principles and Practice* and in 2014 Lippincott published what is considered the reference textbook in interventional radiology titled *Abram's Angiography*.

Dr. Geschwind is a Diplomate of the American Board of Radiology. He is the chairman of the Board of Directors for the World Conference on Interventional Oncology and is the chair of the Interventional Oncology Series from RSNA. Since 2011, Dr. Geschwind has been honored with a 'Top Doctor' award from *US News and World Report*, and he was recognized as one of the 'Top Ten Radiologists' in the United States by *Medical Imaging Magazine*.

Satellite2-2

AASLD/EASL/EORTC Algorithm

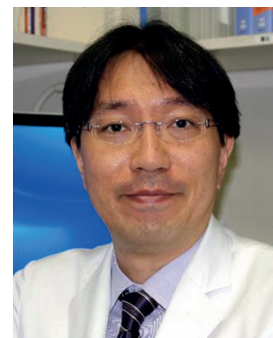
Jean-Francois H. Geschwind

Diagnostic Radiology and Imaging Sciences at Yale University School of Medicine, New Haven, CT, USA

The lecture will cover the importance of imaging in the detection and staging of hepatocellular carcinoma. The guidelines from various societies will be reviewed in detail. It is critically important to understand the recommendations from the societies regarding surveillance and early diagnosis of HCC so prompt intervention can take place, as there is a strong correlation between early intervention and survival. Various imaging methods will be discussed such as the role of ultrasound in early detection, MR imaging as a confirmatory role and CT. Imaging will also be placed in the context of clinical practice worldwide as not all technologies are equally accessible. Despite persisting controversy regarding the guidelines, a clearer picture regarding recommendations for surveillance and imaging diagnosis has emerged and will be presented.

Speaker's Curriculum Vitae

Name Ryosuke Tateishi
Position Project Associated Professor
Institution Graduate School of Medicine,
The University of Tokyo, Tokyo,
Japan



Since 2013, Ryosuke Tateishi has been a Project Associate professor at the Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo where he continues working on diagnosis and treatment of HCC, particularly on those who underwent percutaneous treatment. He has been Board Certified Gastroenterologist of the Japanese Society of Gastroenterology since 2004, Board Certified Hepatologist of the Japan Society of Hepatology since 2007 and General Clinical Oncologist of Japanese Board of Cancer Therapy since 2008. He has been a councilor of the Japan Society of Hepatology and Japanese Society of Gastroenterology since 2012 and 2013, respectively. He is currently a member of Committee for the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Liver Cancer Study Group of Japan and Working Committee for Japanese Clinical Practice Guideline for Liver Cancer.

Research Interest: Etiology, diagnosis and treatment of primary and meta-static liver tumors.

Satellite2-3

Evidence-Based JSH Algorithm

Ryosuke Tateishi

Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

The surveillance and diagnostic algorithm starts from the identification of subjects. Those who have cirrhosis and chronic viral hepatitis are regarded as extremely high risk group. The annual incidence of hepatocellular carcinoma (HCC) in this group is as high as 7–8%. Chronic hepatitis B or C without cirrhosis are considered as high risk group. The annual incidence of HCC is estimated as 3–5% when accompanied with significant fibrosis. Those with liver cirrhosis from any kind of non-viral etiology are also categorized into high risk group. In addition significant risk factors should be taken into account such as age, sex, diabetes mellitus, obesity, alanine aminotransferase, platelet counts, amount of alcohol consumption and hepatitis B virus DNA levels to evaluate the risk of HCC development. The Japanese Guideline recommends different intervals of ultrasonography for the above mentioned risk groups considering the efficiency of surveillance and suboptimal performance of ultrasonography in the extremely high risk group: 3 to 4-month for the extremely high risk group and 6-month interval for the high risk group. In addition periodical examination of three tumor makers is also recommended. When a nodule is detected by ultrasonography, dynamic CT or MRI should be performed. When continuous increase or increase over 200 ng/ml of AFP, increase over 40 mAU/ml of DCP, or increase over 15% of AFP-L3 fraction is observed, dynamic CT or MRI should be considered even when ultrasonography cannot detect any suspicious nodules. When both hyperenhancement in the early phase and washout in the late phase are observed, the nodule can be diagnosed as HCC. When a hyperenhanced nodule lacks late-washout and it is larger than 1 cm, optional examination including EOB-MRI (when the first examination was CT), contrast ultrasonography, and liver biopsy should be considered. Optional examination should also be considered with a hypovascular nodule larger than 1.5 cm. Other suspicious nodules smaller than the above mentioned threshold should be monitored at 3-month interval. When tumor enlargement is observed, dynamic CT or MRI should be performed again.

Speaker's Curriculum Vitae

Name Masumi Kadoya, MD, PhD
Position Professor and Chairman
Institution Dept. of Radiology, Shinshu
University School of Medicine,
Matsumoto, Japan



Masumi Kadoya is currently a Professor and Chairman of Department of Radiology, Shinshu University School of Medicine since 2000. He was born on 1952 in Ishikawa prefecture, Japan. He studied Medicine at Kanazawa University School of Medicine from 1971 and graduated in 1977. Following this, he researched MR imaging as an associated researcher at Department of Radiology, Duke University, USA from 1986 to 1987. He received his PhD degree in Medical Science at Kanazawa University Graduate School of Medicine in 1991.

Professor Kadoya is a board-certified diagnostic radiologist, board-certified interventional radiologist and board-certified gastroenterologist in Japan.

His research interest is abdominal radiology, especially in MR imaging and diagnosis of hepatocellular carcinoma (HCC).

He published over 150 international scientific papers in high quality English Journal and 400 domestic scientific papers.

Satellite2-4

Consensus-Based JSH Surveillance and Diagnostic Algorithm of HCC

Masumi Kadoya¹, Masatoshi Kudo²

¹Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan, ²Department of Hepatology and Gastroenterology, Kinki University, School of Medicine, Osaka, Japan

The Clinical Practice Guideline for the Management of Hepatocellular Carcinoma (HCC) proposed by the Japan Society of Hepatology (JSH) was updated in June 2014 at a consensus meeting of the Liver Cancer Study Group of Japan (LCSGJ). The important update to the diagnostic algorithm is the inclusion of Gd-EOB-DTPA-MRI (EOB-MRI) as a first line surveillance/diagnostic tool.

While surveillance of patients at super-high risk as well as high risk for HCC is essentially performed using ultrasonography (US) or tumor markers according to the JSH guideline, it is recommended that super-high risk patients also undergo dynamic MDCT or MRI every 6 to 12 months to pick up small HCC even when US shows no such evidence of tumor. At institutions specializing in liver cancer in Japan, EOB-MRI is recommended instead of dynamic MDCT even when no tumor is detected on US.

If EOB-MRI shows a hypervascular mass with venous washout, a definitive diagnosis of HCC can be made. If EOB-MRI shows a hypervascular mass without venous washout, a diagnosis of HCC can be made if the mass shows hypointensity in the hepatobiliary phase of EOB-MRI. However, in these cases, a high-flow type hemangioma must be ruled out by another modality. If the mass is isointense or hyperintense in the hepatobiliary phase of EOB-MRI, biopsy is necessary to confirm the diagnosis.

Hypovascular masses on EOB-MRI that are isointense or hyperintense in the hepatobiliary phase can enter the routine surveillance protocol. However, hypointense masses in the hepatobiliary phase have a high potential for malignant transformation, and therefore contrast-enhanced US (CEUS) study using Sonazoid is strongly recommended.

HCC can be correctly diagnosed with Sonazoid CEUS if hypervascularity and/or a defect in the Kupffer phase is observed. Even when a mass is hypovascular on CEUS and there is no defect in the Kupffer phase, hypointensity in the hepatobiliary phase of EOB-MRI is highly suggestive of malignancy. Accordingly, biopsy is recommended for tiny nodules of 1 to 1.5 cm or larger, and differential diagnosis between early HCC and a dysplastic nodule (DN) is necessary. If a mass is diagnosed as a DN or a borderline lesion, intensive follow up is recommended every 3 to 6 months with EOB-MRI (or dynamic MDCT). Intensive follow-up every 3 to 6 months with EOB-MRI is also recommended for tiny nodules smaller than 1 to 1.5 cm.

This algorithm was approved by over 90% of participants and is, therefore, now the new surveillance and diagnostic algorithm recommended by the JSH and LCSGJ.

Satellite 3

Locoregional and Radiation Therapy

Speaker's Curriculum Vitae

Name Shuichiro Shiina
Position Professor
Institution Department of Gastroenterology,
Juntendo University, Tokyo, Japan



Shuichiro Shiina graduated in Medicine at the University of Tokyo in 1982. He completed a residency and fellowship training at the University of Tokyo Hospital and Mitsui Memorial Hospital. He received Ph.D. degree in Medical Science with a study 'A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma (Gastroenterology 2005) at the University of Tokyo in 2005. He moved to Juntendo University in December 2012.

Dr. Shiina has been a pioneer of image-guided percutaneous ablation therapies for liver tumors, such as percutaneous ethanol injection, percutaneous microwave ablation, and radiofrequency ablation. He has performed radiofrequency ablation on over 9,500 patients with liver tumors at the University of Tokyo and Juntendo University.

Dr. Shiina published over 200 International scientific papers in high quality English Journal and over 300 domestic scientific papers. He is a member of The American Gastroenterological Association, Asian Pacific Association for the Study of the Liver, The International Liver Cancer Association, The Japanese Society of Internal Medicine, The Japanese Society of Gastroenterology, The Japan Society of Hepatology, Japan Gastroenterological Endoscopy Society, The Japan Society of Ultrasonics in Medicine, The Japanese Society of Adult Diseases, The Liver Cancer Study Group of Japan, Study Group of Microwave Surgery, The Japan Society of Clinical Oncology, The Japan Pancreas Society, and Japanese Society for Gastroenterological Carcinogenesis and others.

Research Interest: May include key publications of yours.

His research interests are 'Interventional Oncology, such as Radiofrequency Ablation', 'Diagnosis and Treatment of Liver Neoplasms', and 'Chemotherapy of GI tract and Liver Cancers'.

Satellite3-1 (Speech Abstract)

RFA: State of the Art

Shuichiro Shiina

Department of Gastroenterology, Juntendo University, Tokyo, Japan

Only 20 percent of HCC patients are candidates for resection. Furthermore, recurrence is frequent even after apparently curative resection. Liver transplantation is restricted by organ donor shortage.

Thus, various nonsurgical therapies have been introduced. Among these, image-guided percutaneous ablation is considered best for early-stage HCC. Nowadays, most Japanese patients prefer ablation to hepatic resection. Ablation has been widely performed on patients with HCC, generally for those with Child-Pugh class A or B liver dysfunction who have three or fewer tumors each 3 cm or less in diameter.

Ethanol injection was formerly the standard procedure among the various percutaneous ablation techniques. Randomized controlled trials, however, have demonstrated that radiofrequency ablation (RFA) is superior to ethanol injection. RFA had a 46% smaller risk of death (adjusted relative risk, 0.54 [95% CI: 0.33–0.89], $P = 0.02$), and an 88% smaller risk of local tumor progression (relative risk, 0.12 [95% CI: 0.03–0.55], $P = 0.006$) than ethanol injection (Shiina S, et al. *Gastroenterology* 2005).

In our 10-year experience of RFA, final CT showed complete tumor ablation in 2,964 (99.4%) of 2,982 treatments performed for the 1,170 primary HCC patients. With a median follow-up of 38.2 months, 5- and 10-year survival rates were 60.2% (95% CI 56.7% to 63.9%) and 27.3% (95% CI 21.5% to 34.7%), respectively. Multivariate analysis demonstrated that age, anti-HCV, Child-Pugh class, tumor size, tumor number, serum des-gamma-carboxy-prothrombin (DCP) level, and serum lectin-reactive alpha-fetoprotein level (AFP-L3) were significantly related to survival. Five- and 10-year local tumor progression rates were both 3.2% (95% CI 2.1% to 4.3%). Serum DCP level alone was significantly related to local tumor progression. Five- and 10-year distant recurrence rates were 74.8% (95% CI 71.8% to 77.8%) and 80.8% (95% CI 77.4% to 84.3%), respectively. Anti-HCV, Child-Pugh class, platelet count, tumor size, tumor number, serum AFP level, and serum DCP level were significantly related to distant recurrence (Shiina S, et al. *Am J Gastroenterol* 2012).

Various innovations, such as contrast-enhanced ultrasound and multimodality fusion imaging would further improve outcomes in RFA. Sophisticated RFA, which is potentially curative, minimally invasive and easily repeatable for recurrence, would be superior to surgery in the treatment of small- and middle-sized HCC.

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Speaker's Curriculum Vitae

Name Yasuharu Imai, MD, PhD
Position President
Institution Department of Gastroenterology,
Ikeda Municipal Hospital, Japan



Yasuharu Imai, M.D., Ph.D. is currently President of Ikeda Municipal Hospital is also Visiting Professor of Osaka University School of Medicine. He graduated from Osaka University School of Medicine in 1978. He went on to become Assistant Professor of the 2nd Department of Medicine at the Osaka University Graduate School of Medicine for thirteen years. He was also a research fellow at the Royal Free Hospital School of medicine in London. He is widely published and sits on the reviewer board for a number of journals. His special interest includes imaging diagnosis, treatment and prevention of hepatocellular carcinoma.

1978 Graduated from Osaka University School of Medicine
1980–1993 Fellow, Assistant Professor of 2nd Dpt. Of Internal Medicine, Osaka University Graduate School of Medicine
1988–1990 Research fellow, Royal Free Hospital School of Medicine, University of London
1993–2005 Chief, Dpt. Of Gastroenterology, Ikeda Municipal Hospital
2008– Visiting Professor of Gastroenterology, Osaka University School of Medicine
2006– Vice President, Ikeda Municipal Hospital
2013– President, Ikeda Municipal Hospital

Award:

European Radiology – Most Cited Paper 2010 award
Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. Eur Radiol 2010;20:2405–13

Specialty:

Imaging diagnosis, treatment and prevention of hepatocellular carcinoma, Treatment of viral hepatitis.

Satellite3-2

Fusion Imaging Guided RFA

Yasuharu Imai

Department of Gastroenterology, Ikeda Municipal Hospital, Japan

Computed tomography (CT)/magnetic resonance (MR)-ultrasonography (US) fusion imaging system has recently been reported to be useful for radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC). Although US and reference images are usually displayed side-by-side, the overlay function installed in Volume Navigation (GE Healthcare), one of CT/MR-US fusion imaging systems, enables overlapping display of reference images on US. However, background US imaging often becomes too obscure for practical use, because of overlaying different imaging modalities. Subsequently, we developed a novel technique which we call the Extracted-overlay function, in which only an extracted tumor with a visualized ablative safety margin of 5 mm is overlaid on US, and investigated its feasibility for intraoperative evaluation of RFA for HCC.

Seventy-eight HCCs treated by RFA with the Extracted-overlay function were included. After CT or MR imaging data used as a reference were imported into Advantage Workstation Volumeshare 4 (GE Healthcare), a target tumor was extracted from original data and ablative safety margin was added to it. These image data were imported into LOGIQ E9 (GE Healthcare) equipped with Volume Navigation and overlaid on US images, after registration of US and reference images. In RFA, an electrode was inserted targeting the overlaid tumor and margin. After ablation, contrast-enhanced US with Sonazoid (CEUS) was conducted for treatment evaluation. Minimal ablative margins were categorized into 3 groups; (I) <0 mm (protrusion), (II) 0 to <5 mm, and (III) ≥5 mm, by overlaying tumors and margins on perfusion defects of SEUS. Tumors in group I were re-ablated until they were in groups II or III. The categorizations were compared with those by pre- and post-RFA CT-CT/MR-MR fusion imaging, which has been reported to enable accurate treatment evaluation of RFA (Makino et al. Hepatol Res. 2013;43:950–8).

Treatment evaluation by CEUS was impossible in 6 HCCs because of tumor location. Of the remaining 72 HCCs, the numbers of HCCs in groups I, II, and III on CEUS were 2, 63, and 7, respectively. On CT-CT/MR-MR fusion imaging, the numbers of HCCs in groups I, II, and III were 9, 58, and 5, respectively. The categorization of minimal ablative margins by CEUS was compatible with that by CT-CT/MR-MR fusion imaging in 63 tumors (Cohen's quadratic-weighted kappa coefficient 0.60, moderate agreement, $p < 0.01$).

In conclusion, the Extracted-overlay function enables effective treatment planning. Since a target tumor and virtual ablative margin remain visible even during and after ablation, Extracted-overlay function also enables noninvasive and quantitative treatment evaluation just after RFA by combining with CEUS.

Speaker's Curriculum Vitae

Name Shuntaro Obi, MD, PhD
Position Director
Institution Department of Gastroenterology
and Hepatology, Kyoundo Hospital,
Sasaki institute, Tokyo, Japan



Education/Post Graduate Training

College/University:

1985–1991 MD, Teikyo University School of Medicine
May 2007 PhD Gastroenterology Tokyo University School of Medicine #16800

Residency:

1991–1992 Resident in Internal Medicine, Surgery and Anesthesiology, Tama-Hokubu
Medical Center, Tokyo, Japan, Resident in Obstetrics, Gynecology and Pedi-
atrics, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

1992–1993 Resident in Internal Medicine, Tokyo University School of Medicine, Tokyo,
Japan

Fellowship:

1993–1995 Fellow in Gastroenterology, General Hospital National Health Insurance
Asahi Central Hospital, Chiba, Japan

Medical Licensure:

1991 Full Medical License (Japan) #340521

Board Certification:

Jan 1999 Fellow of the Japanese Society of Gastroenterology #29994

Sep 2005 Fellow of the Japanese Society of Internal Medicine #85489

Apr 2010 Fellow of the Japanese Board of Cancer Therapy #09100064

Present Position or Academic Rank:

2006-present Director, Kyoundo Hospital, Tokyo, Japan

2002-present Division Chief, Division of Gastroenterology and Hepatology, Kyoundo
Hospital

2005-present Director, Sasaki Foundation

2008-present Assistant Professor in Gastroenterology, Tokyo University School of Medicine

2009-present Assistant Professor in Gastroenterology Teikyo University School of Medicine

2011-present Assistant Professor in Gastroenterology Kagawa University School of
Medicine

Previous Professional Positions and Appointments:

1995–1998 Staff Physician, Internal Medicine (II), Tokyo University School of Medicine,
Tokyo, Japan

1998–2002 Staff Physician, Gastroenterology, Tokyo University School of Medicine

Honors and Awards:

2009 Fellowship Award from the Foundation for Promotion of Cancer Research

Professional and Society Memberships

Fellowship:

1999 Fellow of the Japanese Society of Gastroenterology

2005 Fellow of the Japanese Society of Internal Medicine

2010 Fellow of the Japanese Board of Cancer Therapy

Membership:

1991 The Japanese Society of Internal Medicine

1993 The Japanese Society of Gastroenterology

1993 The Japanese Society of Hepatology

2007 The Asian Pacific Association of the Study of the Liver

Satellite3-3

Hepatic Artery Infusion Chemotherapy

Shuntaro Obi, Shinpei Sato, Takahisa Sato, Toshihiro Kawai, Takafumi Sugimoto, Miho Kanda

Gastroenterology and Hepatology, Kyoundo Hospital of the Sasaki Institute, Tokyo, Japan

Background: Hepatic arterial infusion chemotherapy (HAIC) is frequently used to treat advanced hepatocellular carcinoma (HCC) in Asian countries. However, there is a lack of evidence supporting the use of HAIC.

Summary: Many studies report high response rates in patients with advanced HCC receiving HAIC, and clinical responses translate to survival benefits. Therefore, prediction of an antitumor response is important in selecting appropriate treatments. There are no proven post-sorafenib therapeutic procedures or procedures for HCC patients with poor liver function, and HAIC is one of the few options for patients in these situations. Despite studies showing its effectiveness, the use of HAIC for treatment of advanced HCC is unclear because convincing data from large-scale randomized clinical trials are lacking. For HAIC to become a standard treatment for HCC, such trials must establish its efficacy compared with other HCC therapies; prediction of antitumor response in HAIC may aid trial design, and a multi-center, open-label, randomized clinical trial of HAIC in advanced HCC is in progress. Optimization of HCC treatment protocols and regimens is also required.

Key Message: HAIC is effective treatments for advanced HCC.

Speaker's Curriculum Vitae

Name Jinsil Seong, MD, PhD
Position Professor
Institution Department of Radiation Oncology,
Yonsei University College of
Medicine, Seoul, Republic of Korea



Professor Jinsil Seong currently works at Department of Radiation Oncology, Yonsei University College of Medicine, Seoul. Prior to her current position, she has been a Visiting Scientist in Department of Experimental Radiotherapy, M.D. Anderson Cancer Center, Houston, USA. She graduated from Yonsei University College of Medicine, Seoul and subsequently completed her PhD degree from Yonsei University, Seoul.

Professor Seong is a former President of Yonsei Liver Cancer Study Group and also a member of various national and international societies including International Liver Cancer Association, Korean Liver Cancer Study Group, European Society for Therapeutic Radiology and Oncology and American Society for Therapeutic Radiology and Oncology. She served as a member of the Editorial Board of International Journal of Radiation Oncology Biology Physics for the past 10 years. Currently she is a council member of Asian Clinical Oncology Society as well as Asia Pacific Primary Liver Cancer Expert Meeting. She is also working as a consultant in International Atomic Energy Agency. Research interest is 'Radiotherapy of HCC' in clinical approach as well as in translational research.

Satellite3-4

Current Status of Radiotherapy in Hepatocellular Carcinoma and How to Maximize Therapeutic Response

Jinsil Seong

Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Management of hepatocellular carcinoma (HCC) has been complex and much varied by new emerging treatment modalities. However, main stream of therapeutic decision is relatively well kept according to the HCC treatment guidelines. While the guidelines from Barcelona Liver Cancer Clinic (BCLC) as well as from National Comprehensive Cancer Network (NCCN) are serving as main ones, Korean Liver Cancer Study Group has made Korean HCC guideline with recent update in 2014.

BCLC system clearly defines treatment modality that can be recommended in each stage; potentially curative therapies for HCC are well established for early stages and sorafenib for advanced stage. Radiotherapy is not included in this guideline. However, there are a plenty of occasion, in which clinical outcome can be further improved with radiotherapy in each subset of BCLC stages. Radiotherapy can either be complementary to weakness of BCLC-recommended treatment or be effective as alone. This notion is well reflected in other guidelines. In NCCN guideline, combination treatment of RT and chemotherapy is recommended either in unresectable but not a transplant candidate or in inoperable local disease. According to the Korean Liver Cancer Study Group (KLCSG) practice guidelines, radiation therapy is considered for unresectable, locally advanced HCC without extrahepatic metastasis, Child-Pugh class A or B, tumors occupying less than two-thirds of the total liver volume, and V_{30Gy} (percentage of liver volume that received a dose of 30 Gy or more) of less than 60% of whole liver.

RADIOTHERAPY category involves many kinds of technology from the basic to high precision level and from electromagnetic (x-ray) to particle beam (proton or heavy ion). Three dimensional conformal radiotherapy (3D CRT), which is now served as a platform RT technique, can also provide a good performance in terms of substantial dose delivery as well as protecting normal tissue through computerized planning that informs dose statistics for both tumor and normal tissues. With a more advanced precision radiotherapy using intensity modulated RT with image guided system, therapeutic benefit can be maximized by escalating RT dose to the tumor while toxicity is kept in acceptable level. However, it is important to check quality control since precision RT requires a learning curve, which might be applied to each member of RT team.

Speaker's Curriculum Vitae

Name Jason Chia-Hsien Cheng
Position Professor
Institution Division of Radiation Oncology,
National Taiwan University
Hospital, Taipei, Taiwan



Professor Cheng is currently a Full Professor at Graduate Institute of Oncology, National Taiwan University College of Medicine, and an Attending Physician and Division Chief at the Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital. He serves as a Principal Investigator of Affiliated Member Site of National Taiwan University Hospital for Radiation Therapy Oncology Group (RTOG). Professor Cheng is also a Panel Member of Asian Consensus Statement for National Comprehensive Cancer Network (NCCN). He is also serving as the Associated Editor of *International Journal of Radiation, Oncology, Biology, Physics* and *Journal of Radiation Oncology*, as well as a journal referee of numerous international journals, such as *Liver International*, *Gastroenterology and Hepatology*, *Hepatology International*, *International Journal of Radiation Oncology, Biology, Physics*, *Radiotherapy and Oncology*, *International Journal of Cancer*, *Journal of Surgical Oncology*, *Radiation Oncology*, *BMC Cancer*, and a number of others.

Research Interest: Radiation oncology, radiation related sensitizer and biomarkers, and radiotherapy related translation research in liver cancer.

Satellite3-5

Advances in Radiation Therapy for Hepatocellular Carcinoma

Jason Chia-Hsien Cheng

Division of Radiation Oncology, National Taiwan University Hospital,
Taipei, Taiwan

External-beam radiation therapy (RT), including photon and proton radiation, has long been integrated into multi-modality treatment for hepatocellular carcinoma (HCC). External RT is used with either long-fractionated treatments or higher dose-per-fraction and fewer fraction-number stereotactic body radiation therapy (SBRT). Fewer fractions of RT require the high demand of precise immobilization, respiratory control, and image guidance for each treatment. Notably, the altered patterns of failure of intra-/extra-hepatic metastasis are less frequently seen with the use of hypofractionated RT or SBRT in 2 weeks compared with long-course RT in 5–6 weeks. The local control of the irradiated hepatic tumor therefore becomes the concern of adding RT into the treatments for HCC. Most patients referred for RT have large-size HCC refractory to ablation or embolization, or tumor invading portal vein or inferior vena cava. Rare complete response and most partial response or stable disease of irradiated tumors indicate the sublethal effect of RT. Higher-intensity RT by higher dose-per-fraction and fewer fraction-number SBRT, and by higher-dose proton therapy are more frequently used to improve the control of irradiated tumor. The demanding need to develop radiation sensitizers, such as histone deacetylase inhibitor, aurora kinase inhibitor, PI3K/mTOR inhibitors, and Sonic Hedgehog inhibitor may be the basis of future clinical trial to further improve the role of RT in HCC treatment. Besides, the appropriate biomarkers, either imaging or serum/plasma biomarkers, may give the early predictive or prognostic signals for better selecting patients and planning further salvage treatment. The proposed RTOG trial to combine RT with sorafenib for advanced-stage HCC and the evolving idea of the trial adding RT adjuvant to incomplete embolization/ablation are pending to provide new knowledge of integrating RT into the HCC treatment guidelines.

Satellite 4

Controversial Issues on Surgical Treatment

Speaker's Curriculum Vitae

Name Ronnie T.P. Poon
Institution Suen Chi-Sun Professor of Surgery
& Chair Professor of Hepatobiliary
& Pancreatic Surgery
The University of Hong Kong



Prof. Ronnie T.P. Poon graduated from the medical school of the University of Hong Kong in 1989 with the award of John Anderson Gold Medal. He also obtained Master of Surgery & PhD degrees from the University of Hong Kong. He received general surgery residency training at St. Vincent's Hospital of Sydney, Australia and Queen Mary Hospital, Hong Kong. After completion of residency training, he specializes in hepatobiliary and pancreatic surgery and joined the Department of Surgery of the University of Hong Kong in 1998 as an Assistant Professor. He was promoted to Associate Professor in 1991, Professor of Surgery in 1996 and Chair Professor in 2011. He is the bearer of Suen Chi-Sun Endowed Professorship. He is currently the Chief of the Division of Hepatobiliary and Pancreatic Surgery at Queen Mary Hospital.

Prof. Poon's main clinical and research interest is in hepatobiliary and pancreatic cancers. In particular, he has devoted much of his research effort on management of liver cancer, ranging from surgical resection or ablation for early cancer to molecular targeted therapy for advanced disease. He has published more than 350 full articles in international journals and delivered over 280 lectures in international conferences on his research work. He has contributed to the establishment of consensus guidelines on management of liver cancer by various international organizations, including Asian-Pacific Association for Study of the Liver and National Cancer Institute of the USA. He is the Founding Board and Governing Council Member of the International Liver Cancer Association, the Chairman of the Scientific Committee of the International Hepato-Pancreato-Biliary Association and Secretary of the Asia-Pacific Primary Liver Cancer Expert Association. He is also the founder and Chairman of the Hong Kong Liver Cancer Foundation.

Prof. Poon has received several awards for his research accomplishment, including the G.B. Ong Traveling Fellowship in 2001, Outstanding Young Researcher Award of the University of Hong Kong in 2003, the International Guest Scholarship of the American College of Surgeons in 2006, Outstanding Researcher Award of the University of Hong Kong 2007 and James IV Traveling Fellowship for 2007. He has served as Associate Editor of the World Journal of Surgery, and he also serves in the editorial board of several surgical, gastroenterology and oncology journals including Cancer Therapy, World Journal of Gastroenterology, HBP Surgery, Journal of Gastrointestinal Surgery and Annals of Surgical Oncology.

Satellite4-1

Optimal Staging and Treatment Stratification for HCC

Ronnie T. Poon

Hong Kong/China

Speaker's Curriculum Vitae

Name Pierce Chow Kah Hoe
Position Council Member
Institution National Cancer Centre Singapore



Pierce Chow is an academic surgeon and Professor at the Duke-NUS Graduate Medical School. He is concurrently Senior Consultant Surgeon at the National Cancer Centre Singapore (NCCS) and the Singapore General Hospital (SGH), and NMRC Senior Clinician Scientist. He co-founded the Asia-Pacific Hepatocellular Carcinoma (AHCC) Trials Group and has been the protocol chair of 5 multi-centre trials. He serves on academic, government and pharmaceutical advisory boards, and has more than 200 scientific publications. He has successfully lead multi-disciplinary teams in translational oncology research and has been protocol chair of multi-national investigator-initiated clinical trials. He was conferred the 2012 NMRC National Outstanding Clinician Scientist Award for his research on Liver Cancer. Professor Chow has been a Council Member of The Asia-Pacific Primary Liver Cancer Expert Association (APPLE) since 2014.

Research Interests: Translational research and clinical trials in hepatocellular carcinoma and steato-hepatitis, the genomics of hepatocellular carcinoma and applications to personalized medicine and outcomes research in hepatopancreato-biliary cancers.

Satellite4-2

The Cost-Utility of Resection versus Transplantation for HCC within the Milan Criteria in Child-Pugh A Patients

Kheng Choon Lim, Vivian W. Wang, Fahad J. Siddiqui, Luming Shi, Edwin S.Y. Chan, Hong Choon Oh, Say Beng Tan, Pierce Chow Kah Hoe

National Cancer Centre Singapore, Singapore

Both liver resection (LR) and cadaveric liver transplantation (CLT) are potentially curative treatments for patients with hepatocellular carcinoma (HCC) within the Milan criteria and with adequate liver function. Adopting either as a first-line therapy carries major cost and resource implications. The objective of this study was to estimate the relative cost-effectiveness of LR against CLT for patients with HCC within the Milan criteria using a decision analytic model. A Markov cohort model was developed to simulate a cohort of patients aged 55 years with HCC within the Milan criteria and Child-Pugh A/B cirrhosis, undergoing LR or CLT, and followed up over their remaining life expectancy. Analysis was performed in different geographical cost settings: the USA, Switzerland and Singapore. Transition probabilities were obtained from systematic literature reviews, supplemented by databases from Singapore and the Organ Procurement and Transplantation Network (USA). Utility and cost data were obtained from open sources. LR produced 3.9 quality-adjusted life years (QALYs) while CLT had an additional 1.4 QALYs. The incremental cost-effectiveness ratio (ICER) of CLT versus LR ranged from \$111,821/QALY in Singapore to \$156,300/QALY in Switzerland, and was above thresholds for cost-effectiveness in all three countries. Sensitivity analysis revealed that CLT-related 5-year cumulative survival, one-time cost of CLT, and post-LR 5-year cumulative recurrence rates were the most sensitive parameters in all cost scenarios. ICERs were reduced below threshold when CLT-related 5-year cumulative survival exceeded 84.9% and 87.6% in Singapore and the USA, respectively. For Switzerland, the ICER remained above the cost-effectiveness threshold regardless of the variations. In conclusion, for patients with HCC within the Milan criteria and Child-Pugh A/B cirrhosis, LR is more cost-effective than CLT across three different costing scenarios: the USA, Switzerland and Singapore.

Speaker's Curriculum Vitae

Name Vincenzo Mazzaferro, MD
Position and Institution Director, Gastrointestinal and Hepato-Pancreatic Surgery and Liver Transplantation Unit
Director, Department of Surgery
Professor, Surgery and Oncology
National Cancer Institute (Istituto Nazionale Tumori IRCCS)



Dr. Mazzaferro is Director of the Gastrointestinal and HepatoPancreatic Surgery and Liver Transplantation Unit and Head of the Department of Surgery at the National Cancer Institute of Milan (NCIM), Italy. He graduated from the University of Turin and gained his Board Certificates in surgery and in oncology at the University of Milan. After a fellowship in clinical oncology at the NCIM, he completed his training in liver surgery and transplantation at the University of Pittsburgh, PA, USA, before joining this institution as Assistant Professor of Surgery. After his return to Milan, he worked as Associate Professor at the Department of Surgery of the NCIM, until he was appointed Director of the Gastrointestinal and HepatoPancreatic Surgery and Liver Transplantation Unit in 2000. This unit is currently widely regarded as the most relevant comprehensive hepato-oncology unit in Italy.

Dr. Mazzaferro is highly regarded for his research in liver transplantation, surgical resection and medical treatment of liver cancer; in 1996 he set a new standard in the selection criteria for liver transplantation in hepatocellular carcinoma (HCC). Since then, the widespread adoption of the 'Milan Criteria' has contributed significantly to the prediction of transplantation outcomes, improving transplant results and organ allocation policies in both Europe and the United States.

Dr. Mazzaferro is Associate Editor of the *Journal of Hepatology* and serves on the Editorial Boards of several distinguished journals. He is Professor of Surgery (contract) and Director of the Training Center of the University of Milan and the Italian Association of Hospital Surgeons. He has published more than 250 articles in high-level, peer-reviewed journals, has authored more than 15 book chapters and delivered more than 265 lectures.

He has also received several national and international awards, including most recently the CIRSE (Cardiovascular and Interventional Radiological Society of Europe) Award in occasion of the Honorary Lecture given during the 2nd European Conference on Interventional Oncology (ECIO 2010), the AACR and Landon Foundation Present INNOVATOR Award and the Milan Ambassador Programme Award in 2009 for his contribution in promoting and advancing knowledge of evidence-based medicine in the management of HCC.

Dr. Mazzaferro is Principal Investigator, co-investigator and grant recipient from public and/or government Institutions such as the American National Institute of Health (NIH), the Italian National Research Council, the Italian Association for Cancer Research and from several private Foundations.

He is a Founding Member of ILCA (International Liver Cancer Association) and member of EASL (European Association Study of the Liver), ESOT (European Society Organ Transplantation), ILTS (International Liver Transplant Society), AASLD (American Association for the Study of Liver Diseases), AISF (Italian Association for the Study of the Liver), SICO (Italian Society of Surgical Oncology), SIGE (Italian Society of Gastroenterology).

Satellite4-3**Changing Perspective for Surgical Treatment of HCC in the Direct Anti-HCV Targets Era***Vincenzo Mazzaferro*

Gastrointestinal and Hepato-Pancreatic Surgery and Liver Transplantation Unit, Department of Surgery, National Cancer Institute (Istituto Nazionale Tumori IRCCS), Milan, Italy

Speaker's Curriculum Vitae

Name Norihiro Kokudo, MD, PhD, FACS
Position Professor and Chairman
Institution Hepato-Biliary-Pancreatic Surgery
Division and Artificial Organ and
Transplantation Division,
Department of Surgery,
The University of Tokyo Hospital,
Tokyo, Japan



Dr. Norihiro Kokudo is the professor and chairman at Hepato-Biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division, Department of Surgery, The University of Tokyo Hospital. He earned his M.D. in 1981, and then Ph.D. in 1988 at University of Tokyo. From 1989 to 1991 he stayed at Department of Surgery, University of Michigan as a visiting research investigator. After 6 years at Cancer Institute Hospital, Tokyo, as a senior staff of GI surgery, he joined the current institution as an associate professor in 2001. He then rose to the current position in 2007. Dr. Kokudo has been conducting a number of research projects on surgical treatment of HCC, colorectal liver metastases, and living donor liver transplantation. As the chairman of the guideline committee, he compiled 3rd version of Japanese clinical practice guidelines for HCC in 2013. Dr. Kokudo is currently the president of Japan Surgical Society and the president of Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA). He is a member-at-large of International Hepato-Pancreato-Biliary Association (IHPBA), and a governing board member for ILCA. He is also a fellow of American College of Surgeons, and a member of International Society of Surgery and The Society of Surgical Oncology. He is an honorary regional editor for HPB, and an associate editor for Liver Cancer and Japanese Journal of Clinical Oncology. He is on the editorial board of Annals of Surgery, World Journal of Surgery, Journal of HPB Science, and Hepatogastroenterology.

Satellite4-4

Treatment of Recurrent HCC after Resection

Norihiro Kokudo, Kiyoshi Hasegawa, Yoshihiro Mise, Suguru Yamashita, Satoshi Yamamoto, Yoshikuni Kawaguchi, Nobuhisa Akamatsu, Junichi Arita, Junichi Kaneko, Yoshihiro Sakamoto

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Backgrounds: Although the efficacy of hepatic resection for HCC has been confirmed, high recurrence rate up to 70% at 5 years after surgery remains an unsolved problem. The previous reports suggested that second resection would be also effective for the first recurrence, however, the feasibility and efficacy of third or more resection have not been adequately assessed.

Methods: From November 1994 to November 2011, consecutive 1,007 patients with HCC underwent 1,340 curative hepatic resection at the Tokyo University Hospital. Among them, 941, 289, and 110 underwent the first, second, and third or more resection, respectively. The criteria of repeated resection for recurrence have been the same to the one for a primary HCC.

Results: The median operation time was 6.4 hours in the third or more resection group, which was significantly longer than in the second resection group (median, 5.9 hours). The incidence of bile leakage and wound infection were more frequent in the third or more resection group than the second resection group (12.5% vs. 6.2%, [$P = 0.04$] and 2.9% vs. 0.4% [$P = 0.03$], respectively). The 3-year and 5-year disease-free survival rates were 36.8% and 27.1% after the first resection, 24.4% and 17.9% after the second resection, and 26.1% and 12.8% after the third or more resection, respectively ($P < 0.01$ [first vs. third or more resection], $P = 0.95$ [second vs. third or more resection]). The 5-year overall survival rates from each.

Resection were similar among the groups (65.3%, 60.5%, 68.2%, respectively).

Conclusion: The third or more repeated resection is also safe and feasible with sufficient long-term survival as well as the second resection, although longer operation time and higher morbidity rates. If resection is possible considering of tumor- and liver function-related factors, repeated resection is regarded as the standard choice for recurrence of HCC.

Speaker's Curriculum Vitae

Name Feng Shen
Position Vice President and Chief Surgeon
Institution Shanghai Eastern Hepatobiliary
Surgery Hospital, Shanghai, China



Professor Shen Feng is the vice president and chief surgeon of Shanghai Eastern Hepatobiliary Surgery Hospital. He received his M.D. in Institute of Hepatobiliary surgery affiliated to Second Military Medical University and completed his postdoctoral fellowship in the Department of Pathology at Massachusetts General Hospital in Boston and Department of General Surgery at Rush Presbyterian St. Luke's Medical Center in Chicago.

Dr. Shen's clinical interests include benign and malignant diseases of the liver, with a special interest in the surgical therapy of hepatocellular carcinoma (HCC). Dr. Shen also has an interest in the management of intrahepatic cholangiocarcinoma (ICC). Dr. Shen has published 39 articles on *JCO*, *Hepatology*, *Gut* et al. as first or corresponding author.

Dr. Shen is the principal scientist of National Key Project for Comprehensive Treatment of Liver Cancer, vice director of China Medical Association Surgery Branch Hepatology Group, vice chairman of Chinese Society of Liver Cancer, vice chairman of the Society of Hepatobiliary Surgery of PLA, vice chairman of Shanghai Society of General Surgery, member at large of International Hepato-Pancreato Biliary Association and secretary of Asian-Pacific Hepato-Pancreato-Biliary Association.

Satellite4-5

A Prognostic Scoring System for Patients with Multiple Hepatocellular Carcinomas Treated by Hepatectomy

Feng Shen

Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China

Background: The selection criteria of hepatectomy for patients with multiple hepatocellular carcinomas (HCCs) remain controversial.

Methods: A scoring system based on preoperative data and independent predictors of overall survival (OS) was developed in a primary cohort of 510 patients who underwent hepatectomy for multiple HCCs from 1998 to 2006, and validated in 177 patients who were operated from 2006 to 2009 at the Eastern Hepatobiliary Surgery Hospital.

Results: In the NDR scoring system, tumor number (N) >3, total tumor diameter (D) >8 cm, and a ratio of largest/smallest diameter (R) >6 were independent predictors of OS. Its predictive accuracy as determined by the area under the curve (AUC, 0.718) was larger than the four conventional staging systems (0.524–0.662). It stratified postoperative OS into five levels (0–4 score). The 5-year OS rate of patients with a NDR score 0–2 was 46.5% versus 13.9% in those >2 ($P < 0.001$). Patients with a score 0–2 therefore were recommended for hepatectomy. The feasibility of this NDR score 0–2 was compared with the previously reported criteria. If the two more stringent inclusion criteria were adopted, 45.5–75.7% of patients with a NDR score 0–2 would be excluded, but their 5-year OS rates were comparable to those within the criteria (44.7% vs. 52.1%, $P = 0.083$; 46.6% vs. 46.3%, $P = 0.674$). If the less stringent criteria were used, an additional 25.9% of patients received hepatectomy, but their 5-year OS rate was 13.9%.

Conclusions: The NDR scoring system was more accurate in selecting patients with multiple HCCs for hepatectomy.

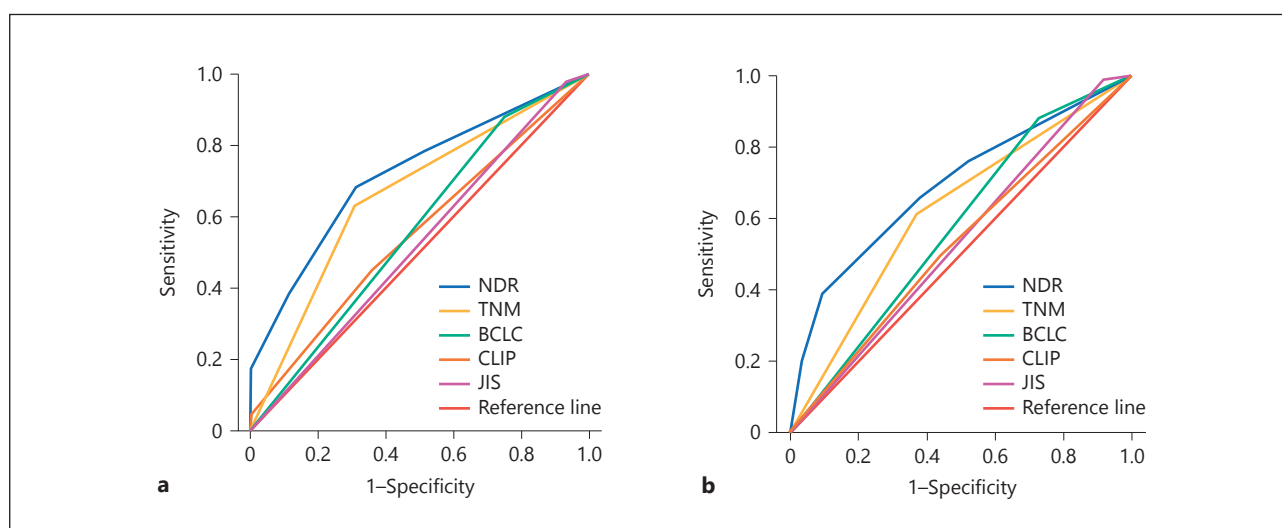


Fig. 1. AUCs of the NDR score system and the other staging system to predict overall survival in the primary (a) and validation (b) cohorts. NDR scoring system of tumor number (N), total tumor diameter (D), and the ratio of the largest diameter

to the smallest diameter (R); TNM 6th edition of TNM/AJCC staging system. BCLC = Barcelona Clinic Liver Cancer system; CLIP = Cancer of the Liver Italian Program; JIS = Japan Integrated Staging Score.

Speaker's Curriculum Vitae

Name Ghassan K. Abou-Alfa
Position Associate Professor
Institution Gastrointestinal Oncology Service
at Memorial Sloan Kettering Cancer
Center and Weill Cornell Medical
College, New York, NY, USA



Dr. Ghassan K. Abou-Alfa is an associate professor of the Gastrointestinal Oncology Service at Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College in New York. Dr. Abou-Alfa specializes in the treatment of gastrointestinal malignancies and in particular, hepatocellular carcinoma and biliary cancers. Dr. Abou-Alfa received his medical degree from the American University of Beirut, Lebanon, and completed his post-doctoral training at Yale University School of Medicine. His research is dedicated to finding novel therapies and improving the effectiveness current therapies for hepatocellular carcinoma and biliary cancers, while continuing to understand the basic mechanisms of the diseases and their therapies. Dr. Abou-Alfa has many publications in the field. He led on many occasions, international teams of investigators, and published the first report on the effective role of the novel agent sorafenib in the treatment of primary liver cancer and the role of adding doxorubicin to sorafenib. One of Dr. Abou-Alfa key interests is developing therapeutic strategies that help overcome resistance to sorafenib. Dr. Abou-Alfa serves as the chair of the National Cancer Institute (NCI) Task Force for Hepatobiliary Cancers and the chair of the AIDS Malignancy Consortium (AMC) Non-AIDS Defining Malignancies (NADC) Liver/GI Task Force. Dr. Abou-Alfa also chairs the hepatocellular carcinoma subgroup of the Alliance cooperative group, and is a cadre member of both the gastrointestinal cancers and pharmacogenomics and population pharmacology committees. Dr. Abou-Alfa who has lectured worldwide on the subject on gastrointestinal malignancies, is also a strong advocate for raising awareness and support for improving the outcome of patients with this disease, and enhancing oncologic education worldwide.

Satellite4-6

Systemic Plus Local Therapy for Advanced HCC

Ghassan K. Abou-Alfa

Memorial Sloan Kettering Cancer Center, New York, NY, USA

The combination of systemic therapy – precisely anti-angiogenic – plus loco regional therapies such as transarterial chemoembolization (TACE) for the treatment of unresectable hepatocellular carcinoma (HCC) has failed so far as a strategy to circumvent local recurrence of disease. The biology supports a continuous approach of delivering antiangiogenic therapy in combination with TACE, with the intent of inhibiting the surge of VEGF that occurs immediately after embolization. Two randomized studies have failed to show a clinically meaningful improvement in outcome when TACE has been combined with sorafenib. A phase III study examining the sequential approach of sorafenib after TACE in Japanese and Korean patients with unresectable HCC failed to demonstrate prolongation of time to progression (TTP) when sorafenib was administered after TACE. More than 50% of patients in the experimental arm started sorafenib more than 9 weeks after TACE, with 73% of the patients requiring dose reduction. The authors concluded that these factors may have influenced the results of their study. The randomized phase II SAPCE study evaluated TACE with DEBDOX in combination with sorafenib or placebo administered 3–7 days before TACE and given continuously. The primary end point, median TTP determined by independent reviewers, was identical in the two arms: 169 days with sorafenib vs. 166 days with placebo, although the study was formally positive, given the predefined exploratory α of 0.15 (HR, 0.797; 95% CI, 0.588– 1.080; $P = 0.072$). There was no difference in overall survival (HR, 0.898; 95% CI, 0.606–1.330; $P = 0.295$).

Such approach is not justified either for use in the metastatic setting either. A retrospective analysis of 243 HCC patients treated with hepatic arterial embolization at Memorial Sloan Kettering Cancer Center over a seven-year period identified 36 patients with metastatic disease, of whom 22 received embolization only, while 14 received trans-arterial embolization (TAE) plus systemic therapy at some time during their whole treatment course. The analysis demonstrated that those patients with metastatic HCC who underwent TAE alone had a median OS of 5.8 months (95% CI 4.1 to 11.0) while those that received sorafenib with TAE had a median OS of 19.3 months (95% CI 3.7 to 66.7).

Further studies of combined modality therapy in the setting of metastatic HCC may be warranted.

Satellite 5

New Aspects of Liver Transplantation

Speaker's Curriculum Vitae

Name Nobuhisa Akamatsu
Position Lecturer and Supervisory Surgeon
Institution Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan



Academic Degrees:

M.D. Tokyo University School of Medicine in 1997
Ph.D. Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo in 2006.

Professional Experiences:

- Surgical resident at Tokyo University Hospital- June 1997 to May 1999.
- Regular surgical stuff at Takeda General Hospital in Fukushima- June 1999 to May 2001.
- Senior surgical resident at Artificial Organ and Transplantation Division, Department of Surgery, Tokyo University Hospital- June 2001 to May 2005.
- Attending surgeon at Department of Hepato-biliary-pancreatic Surgery, Saitama Medical Center, Saitama Medical University- June 2005 to June 2008.
- Lecturer and supervisory surgeon at Department of Hepato-biliary-pancreatic Surgery, Saitama Medical Center, Saitama Medical University- July 2008 to September 2013.
- Lecturer and supervisory surgeon at Artificial Organ and Transplantation Division, Department of Surgery, Tokyo University Hospital- October 2013 to present.

Professional Specialty:

Liver Transplant and Hepato-biliary-pancreatic Surgery

Professional Society:

Member of:

The Japan Surgical Society
The Japanese Society of Hepato-biliary-pancreatic Surgery
The Japanese Society of Gastroenterological Surgery
The Japanese Liver Transplantation Society

Main Surgical Interests:

Liver transplantation, Hepato-biliary-pancreatic Surgery

Main Research Interests:

- 1) Liver transplantation
- 2) Hepatocellular carcinoma
- 3) Hilar cholangiocarcinoma

Satellite5-1

Living-Donor vs. Deceased-Donor Liver Transplantation for Patients with Hepatocellular Carcinoma

Nobuhisa Akamatsu, Yoshihiro Sakamoto, Norihiro Kokudo

Artificial Organ and Transplantation Division, Department of Surgery,
Graduate School of Medicine, University of Tokyo, Tokyo, Japan

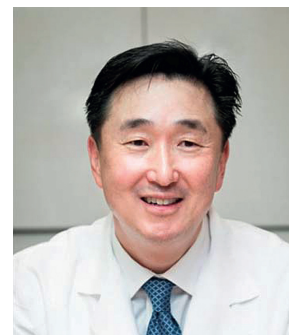
With the increasing prevalence of living-donor liver transplantation (LDLT) for patients with hepatocellular carcinoma (HCC), some authors have reported a potential increase in the HCC recurrence rates among LDLT recipients compared to deceased-donor liver transplantation (DDLT) recipients. The aim of this presentation is to encompass current opinions and clinical reports regarding differences in the recurrence of HCC, between LDLT and DDLT.

While some studies report impaired recurrence-free survival and increased recurrence rates among LDLT recipients, others, including large database studies, report comparable outcomes between LDLT and DDLT. Studies supporting the increased recurrence in LDLT have linked graft regeneration to tumor progression, but we found no association between graft regeneration/initial graft volume and tumor recurrence among our 131 consecutive LDLTs for HCC cases. Among 131 LDLTs for HCC, HCC recurrence was observed in 11 patients, and overall survival at 1, 3, and 5 years was 88%, 82%, and 76%, respectively. The graft volume/standard liver volume at LDLT and the graft regeneration rate at 3 months were $46 \pm 9\%$ and $90 \pm 24\%$ in 11 patients with recurrence, respectively, which were comparable to 120 patients without recurrence ($47 \pm 9\%$ and $93 \pm 34\%$, respectively). The independent predictors for HCC recurrence in our series were tumors not within the 5-5 rule ('up to 5 nodules with a maximum tumor diameter within 5 cm', Tokyo criteria), AFP level over 400 ng/ml, and des-gamma-carboxy prothrombin levels over 200 mAU/ml.

In the absence of a prospective study regarding the use of LDLT versus DDLT for HCC patients, there is no evidence to support the higher HCC recurrence after LDLT than DDLT, and LDLT remains a reasonable treatment option for HCC patients with cirrhosis.

Speaker's Curriculum Vitae

Name Kyung-Suk Suh
Position Professor and Chairman
Institution Department of Surgery Seoul
National University College of
Medicine, Republic of Korea



Professor Suh graduated Seoul National University Medical College in 1984. After finishing residentship and fellowship at the Department of Surgery, Seoul National University Hospital, he joined same Department as a Faculty staff. He is currently a Professor and Chairman at the Department of Surgery, Seoul National University College of Medicine. He is now chairman of the Korean Liver Cancer Study Group and President of the Korean Association of Hepato-biliary-pancreas Surgery. He has main interest in liver surgery including liver transplantation. As a pioneer in the field of liver transplantation, he developed many new techniques and published many clinical papers. Now, he is a principal investigator in several nation-wide multi-center studies associated with liver transplantation and surgical treatment of HCC.

Research Interest:

Prognostic factor and tumor maker for HCC
HCC pathogenesis in the fatty liver
Liver transplantation for the advanced HCC
New technique in living donor liver transplantation

Satellite5-2**Graft Steatosis in Living Donor Liver***Kyung-Suk Suh*

Seoul National University College of Medicine, Seoul, Republic of Korea

Living donor liver transplantation (LDLT) is the predominant form of liver transplantation, especially in countries where cadaveric donors are scarce. Consequently, suboptimal donor livers such as steatotic livers are sometimes unavoidably used for transplantation given the limited number of donor candidates for LDLT. There are two type of fatty infiltrations, macrovesicular steatosis (MaS) and microvesicular steatosis (MiS). The clinical importance of MiS remains controversial. Grafts with severe steatosis are frequently associated with primary graft nonfunction, delayed graft function, and postoperative morbidity in deceased donor LT (DDLTL).

Liver biopsy, the current standard of reference for the assessment of steatosis, is invasive, has sampling errors, and is not appropriate in some settings. Several magnetic resonance (MR) imaging such as chemical shift imaging and MR spectroscopy are currently in clinical use for the detection and quantification of fat.

Major concerns using grafts with steatosis in the LDLT setting is the influence of the presence of steatosis on the risks of liver resection in an otherwise healthy donor, and on the regenerative capabilities of the remnant liver. Consecutive 54 living liver donors from September 2002 to December 2003 in my center were prospectively evaluated and were allocated according to histologic degree of macrovesicular steatosis: Group 1, <5% (n = 36); Group 2, 5–30% (n = 18). The results of serial liver function test, and major and minor morbidities were comparable between groups. No difference in the rate of liver regeneration at 10 days after hepatectomy was found between the groups ($P = 0.487$), but the liver regeneration rate at 3 months after hepatectomy in Group 1 was slightly higher than that in Group 2 ($P = 0.044$). Subsequently, no difference was observed between the two groups at 1 year after hepatectomy ($P = 0.400$). Mild hepatic steatosis is immediately cleared after hepatectomy and early regeneration power is impaired, but long-term regeneration power is comparable. And, hepatectomy in donors with mild steatosis can be performed with low morbidity.

In contrast to DDLT, hepatic regeneration power is inevitably necessary in the recipient who undergoes LDLT. Between September 2002 and February 2004, 55 cases of LDLT with a liver biopsy performed postoperative 10th day were enrolled. Patients were grouped according to the intraoperative histologic degree of macrovesicular steatosis (MaS) as follows: Group 1, <5% (n = 24); Group 2, 5–15% (n = 24); Group3, 15–30% (n = 7). The number of positively stained hepatocytes in 10 high power fields was 48.0 ± 17.1 , 53.8 ± 14.4 , and 51.5 ± 4.1 in each group by PCNA ($P = 0.681$), and 24.0 ± 14.0 , 25.5 ± 11.8 , and 21.6 ± 6.8 by Ki-67 ($P = 0.825$), respectively. No primary graft nonfunction or delayed graft function occurred. Major complications were comparable among groups. Hepatic regeneration power was not impaired in grafts with less than 30% of MaS.

Nonalcoholic steatohepatitis (NASH) is a relatively new disease entity representing no history of alcohol abuse but with liver biopsies demonstrating fatty change, lobular inflammation, focal necrosis, and Mallory bodies consistent with alcoholic hepatitis. There was one reported death in live donor with NASH. It is important to differentiate the NASH from nonalcoholic fatty liver disease (NAFLD).

Fortunately, fatty liver disease is a reversible disease. So whenever we encounter a fatty liver donor, we have to treat this potential donor preoperatively as long as the recipient's condition allows. Diet program and exercise can reduce the amount of steatosis effectively in relatively short period.

In LDLD, the donor safety is primary concern and so, fatty liver disease should be evaluated meticulously in live donors. Long-term outcome of donors with fatty liver disease should be studied more.

Speaker's Curriculum Vitae

Name Ming-Chih Ho, MD, PhD
Position Associate Professor
Institution Department of Surgery, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan



Ming-Chih Ho received his M.D. degree from National Taiwan University, School of Medicine, and his Ph.D. degree in Surgery from Institute of Clinical Medicine, National Taiwan University College of Medicine. He is currently an Associate Professor in the Department of Surgery, National Taiwan University College of Medicine and National Taiwan University Hospital. His current research interest focuses primarily on liver cancer, liver transplantation and medical ultrasound.

Satellite5-3**Liver Resection or Liver Transplantation for Early Hepatocellular Carcinoma***Ming-Chih Ho, Cheng-Maw Ho, Rey-Heng Hu, Yao-Ming Wu, Po-Huang Lee*

Department of Surgery, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan

Liver resection and transplantation are the treatment for cure of early HCC. In patients with underlying liver disease, the abnormal liver parenchyma is completely removed with the tumor during transplantation. This potentially precludes the possibility of recurrent HCC in the residual liver. However, higher surgical mortality and morbidity, complications of immunosuppressant and donor shortage are the main drawbacks of liver transplantation. The decision to choose liver transplantation or resection for early HCC remains debatable.

In our previous study, the overall and recurrence free survivals were compared between patients underwent liver resection versus transplantation for HCC within UCSF criteria. The resection group had similar patient survival rate to the transplant group but statistically higher recurrent rate. Cirrhotic patient receiving surgical resection had significantly worse patient survival and recurrence free survival in compared with non-cirrhotic patients receiving liver resection and patients receiving liver transplantation. Recently, a large series study from US showed better overall survivals at 5 and 10 years for transplantation patients, with greater differences in disease-free survival regardless of age ≤ 70 years or presence of cirrhosis.

In patients with well compensated cirrhosis, resection is usually chosen as the first line treatment. However, the unresected liver parenchyma bears the risk of developing a new HCC. Increased tumor size and number, microscopic venous invasion, poor differentiation grade, higher α -fetoprotein levels and des- γ -carboxy prothrombin levels are associated with higher risk of recurrence after both liver resection and transplantation. These factors cannot be used as selection criteria for resection or transplantation. A predictor of extrahepatic HCC dissemination which can differentiate HCC with or without systemic spread may be helpful to estimate the possible benefit of complete liver removal by liver transplantation.

Tumor recurrence after resection usually leads to the poor outcomes of HCC patients. Salvage liver transplantation may be used as a solution to rescue the patients. Amount 102 recurrent HCC patients whose initial tumor statuses at index hepatectomy were within Milan's criteria, 35 had recurrent tumor beyond Milan's criteria. Large tumor size and short disease free interval are associated with the recurrence beyond Milan's criteria. Our study implied only small percentage of patients may lose the chance of cure when resection was performed as the first line treatment. In addition, liver transplantation may be omitted in patients without HCC recurrence.

In summary, both liver resection and transplantation provides the best survival for patients with early HCC. Transplantation has better overall and disease free survival than resection especially in patients with liver cirrhosis. Liver transplantation is recommended for early HCC patients with significant liver cirrhosis or when liver functional reserve is unable to tolerate liver resection. Liver resection can be chosen when the residual liver is relatively healthy or when transplantation cannot be performed on time. Salvage liver transplantation may serve as a secondary treatment for patients with HCC recurrence after resection.

Speaker's Curriculum Vitae

Name Toshimi Kaido, MD, PhD
Position Associate Professor
Institution Dept. of Hepato-Biliary-Pancreatic and Transplant Surgery, Kyoto University, Kyoto, Japan



Education:

1987 Graduated from Kyoto University
1996 Graduated from Graduate School of Medicine, Kyoto University

Career:

1998–1999 Research associate, Institute for Frontier Medical Sciences, Kyoto University
1999–2001 Assistant Professor, First Department of Surgery, Kyoto University
2001–2007 Department of Surgery, Otsu Municipal Hospital
2007–2009 Assistant Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Kyoto University
2009-Sep 2014 Associate Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Kyoto University
Oct 2014~ Associate Professor, Head of Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Kyoto University

Board Certification:

Board Certified Surgeon of the Japanese Surgical Society
Board Certified Surgeon of the Japanese Society of Gastroenterological Surgery
Board Certified Surgeon of the Japanese Society of Hepato-Biliary-Pancreatic Surgery
Board Certified Hepatologist of the Japan Society of Hepatology
Board Certified Surgeon of the Japan Society for Transplantation

Awards (after 2007 only):

2007 President award of the 19th Meeting of the Japanese Society of Hepato-Biliary-Pancreatic Surgery
2008 Chairman award of the 20th Meeting of the Japanese Society of Hepato-Biliary-Pancreatic Surgery
Best subject award of the 21th Annual Meeting of Japan Society for Surgical Infection
Excellent poster award of Japan Digestive Disease Week 2008
2009 Best subject award of the 45th Annual Meeting of the Japan Society of Hepatology
2012 Fellowship award of Japanese Society for Parenteral and Enteral Nutrition (JSPEN)
2013 The best paper of the 15th AJINOMOTO Award of the Japan Society of Hepatology
The Best Paper in The Year of Japanese Society for Parenteral and Enteral Nutrition (JSPEN)
2014 Best Oral Award of International Hepato-Pancreato-Biliary Association (IHPBA)

Research Interest:

Innovations in Hepato-Biliary-Pancreatic and Transplant Surgery, LT for HCC, Perioperative management including nutrition and infection

Satellite5-4

Impact of Sarcopenia in Liver Surgery

Toshimi Kaido, Shinji Uemoto

Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Skeletal muscle depletion and decrease in muscle strength, referred to as sarcopenia, predicts morbidity and mortality in patients undergoing digestive surgery. However, the impact on liver surgery is unclear. The present study investigated the impact of sarcopenia on patients undergoing living donor liver transplantation (LDLT) and liver resection for hepatocellular carcinoma (HCC).

LDLT study 1: Sarcopenia was assessed by a body composition analyzer (InBody 720®) in 124 adult patients who underwent LDLT between February 2008 and April 2012. The correlation of low skeletal muscle mass with Child-Pugh classification and MELD score, the impact of skeletal muscle mass on survival after LDLT, the effect of perioperative nutritional therapy and perioperative risk factors for poor survival were retrospectively analyzed. The median ratio of preoperative skeletal muscle mass was 92% (range 67%–130%) of the standard mass. Preoperative skeletal muscle mass did not correlate with the branched-chain amino acids to tyrosine ratio ($r = -0.254$, $p = 0.005$) and body cell mass ($r = 0.636$, $p < 0.001$). The overall survival rate in patients with low skeletal muscle mass was significantly lower than in patients with normal/high skeletal muscle mass ($p < 0.001$). Perioperative nutritional therapy significantly increased overall survival in patients with low skeletal muscle mass ($p = 0.009$). Multivariate analysis showed that low skeletal muscle mass and lack of perioperative nutritional therapy were found to be risk factors for death after transplantation.

LDLT study 2: Based on the results of study 1, we have revised our inclusion criteria for LDLT since January 2013 except acute liver failure. We added 'who can walk alone' to our criteria and started preoperative rehabilitation as well as nutritional therapy aggressively. Fifty-five consecutive adult patients who underwent LDLT between January 2013 and December 2014 were enrolled in this study. We defined patients with sarcopenia as those with low skeletal muscle mass and low handgrip strength. The impact of pretransplant sarcopenia on patient survivals and sequential changes in sarcopenic parameters (skeletal muscle mass and muscle strength) were prospectively analyzed. One-year overall survival rate in all patients was 94%. The overall survival rate in patients with sarcopenia ($n = 9$) was significantly lower than in patients without sarcopenia ($n = 46$) ($p = 0.002$). SMM worsened after LDLT and did not recover to preoperative levels until 1 year after LDLT. In contrast, handgrip strength recovered to preoperative levels at 6 months after LDLT following sharp decrease at 1 month after LDLT.

LDLT study 3: Next, we newly focused on muscle quality, namely muscle steatosis, as well as muscle quantity. The intramuscular adipose tissue content (IMAC) and psoas muscle mass index (PMI) were evaluated by preoperative CT in 200 adult patients undergoing LDLT between January 2008 and October 2013. We investigated the impact of these parameters on outcomes. The overall survival rates in patients with high IMAC or low PMI were significantly lower than in patients with normal IMAC or PMI ($P < 0.001$, $P < 0.001$, respectively). Multivariate analysis showed that high IMAC and low PMI were independent risk factors for death after LDLT.

HCC study: We similarly investigated the impact of IMAC and PMI on outcomes after hepatectomy for HCC in the latest 477 patients. The overall and recurrence-free survival rates were significantly lower in patients with high IMAC than in patients with normal IMAC ($P < 0.0001$, $P = 0.0012$, respectively). In contrast, the overall and recurrence-free survival rates were not significantly different between patients with high PMI and low PMI. On multivariate analysis, high IMAC was an independent risk factor for death and HCC recurrence after hepatectomy together with other known risk factors.

In conclusion, preoperative sarcopenia has a strong impact on outcomes in liver surgery.

Satellite 6 Reappraisal of TACE

Speaker's Curriculum Vitae

Name	Riccardo Lencioni, MD, FSIR, EBIR
Position	Professor and Director
Institution	Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy



Riccardo Lencioni, MD, FSIR, EBIR, is board certified in Radiology and Gastroenterology. He is Professor and Director of Diagnostic Imaging and Intervention at Pisa University School of Medicine in Pisa, Italy.

Professor Lencioni is one of the world's foremost interventional oncology specialists, known especially for his highly influential work in liver cancer. He has been a leading member of several expert panels developing recommendations for research and clinical management of hepatocellular carcinoma. He has co-authored the white papers *Design and Endpoints in Clinical Trials in Hepatocellular Carcinoma* (2008), *Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma* (2010), and *EASL-EORTC Clinical Practice Guidelines: Management of Hepatocellular Carcinoma* (2012).

Riccardo Lencioni is the Chairman of the World Conference on Interventional Oncology. He is a co-Founder of the International Liver Cancer Association, in which he also acts as the Executive Secretary. He is an Associate Editor of the journal *Liver Cancer* and serves as an editorial board member or reviewer for several other titles.

Riccardo Lencioni has published 182 articles in peer-reviewed international journals indexed in PubMed and numerous chapters in textbooks of interventional radiology, gastroenterology, oncology and surgery. In addition, he has been the editor of nine books. According to the SCOPUS database, citations of his publications currently number in excess of 13,000 with an *h* index of 53. Riccardo Lencioni has been an invited or honorary lecturer at more than 450 international meetings or conferences.

Satellite6-1

Lipiodol TACE and DEB-TACE: Evidence and Practice

Riccardo Lencioni

Division of Diagnostic Imaging and Intervention, Pisa University School of Medicine, Pisa, Italy

TACE is the most widely used treatment for HCC patients unsuitable for radical therapies worldwide. The data collected in the GIDEON, the largest global observational study completed in the field of HCC clinical management so far, suggests that nearly half of all HCC patients receive TACE at some timepoint in the course of the disease. Conventional TACE regimens are based on the administration of an anticancer-in-oil emulsion followed by embolic agents. The key component of this procedure is Lipiodol, which is used both as a vehicle to carry and localize the chemotherapeutic agent inside the tumor and as an embolic agent for tiny tumor vessels. The introduction of embolic, drug-eluting beads has provided an alternative to Lipiodol-based regimens. Experimental studies have shown that TACE with drug-eluting beads has a safe pharmacokinetic profile and results in effective tumor killing in animal models. Clinical experiences have confirmed that drug-eluting beads provide a combined ischemic and cytotoxic effect locally with low systemic exposure. In a multicenter study including 201 European patients, DEB-TACE resulted in a significant reduction in liver toxicity and drug-related adverse events compared with conventional TACE. However, the randomized trials completed so far failed to show statistically significant differences in objective response or overall survival between DEB-TACE and conventional TACE. Recent advances in drug eluting bead technology include the development of smaller and inherently radio-opaque microspheres. In experimental settings, such tiny beads were shown to allow for more concentrated drug delivery within the tumor and greater tumoral devascularization. Further investigation is warranted to understand the clinical benefit associated with these novel embolization strategies.

Speaker's Curriculum Vitae

Name Yasuaki Arai
Position Director of the Hospital
Chair, Department of Diagnostic
Radiology
Institution National Cancer Center Hospital,
Tokyo, Japan



Yasuaki Arai is currently a director of National Cancer Center hospital (NCCH) since 2013, and the president of Japanese Society of Interventional Radiology (JSIR) since 2014. He is also a chair of Department of Diagnostic Radiology, NCCH, and a chair of Japan Interventional Radiology in Oncology Study Group (JIVROSG) since 2002.

Engaging in interventional radiology, Dr. Arai has introduced some new devices and technique such as implantable catheter and port system for hepatic arterial infusion chemotherapy and Angio-CT system. Also, he organized JIVROSG to pursue clinical trials and have led over 30 clinical trials of interventional radiology.

He is an Associate Editor of several leading journals, including Journal of Vascular & Interventional Radiology. He also holds some important positions of committees in Ministry Health, Labor and Welfare (MHLW) and Pharmaceuticals and Medical Device Agency (PMDA).

Research Interest: Oncology, Interventional radiology, Clinical trial.

Satellite6-2

Lipiodol TACE and DEB-TACE: Which One to Which Patient?

Yasuaki Arai

Department of Diagnostic Radiology, National Cancer Center Hospital,
Tokyo, Japan

Various results have been reported from clinical trials of Lipiodol TACE and DEB-TACE for HCC, however, there is no comparative study concluding which embolic material is superior to another. The past results have been led from the outcomes in groups of patients with various backgrounds, and we can some characteristics as follows:

1. There is no clear evidence about the role of anti-cancer agent in TACE. (Ib) (Cardiovasc Intervent Radiol 33:541–51, 2010).
2. Selective manner leads to better survival outcome in Lipiodol TACE. (IIb) (Jpn J Radiol 30:560–6, 2012).
3. CR rate is 30–60% by superselective Lipiodol TACE for hypervascular HCC less than 5 cm. (III) (J Hepatobiliary Pancreat Sci 17:407–9, 2010).
4. Overall survival by DEB-TACE for selected patients group is 48.6 months. (III) (J Hepatol 56:1330–5, 2012).
5. Overall survival by Lipiodol TACE (Asian style) is 3.1 year. (IIa) (J Vasc Interv Radiol 24:490–500, 2013).
6. There is no significant difference of response rate and overall survival between Lipiodol TACE and DEB-TACE. (Ib) (Br J Cancer 15:111:255–64, 2014).
7. DEB-TACE shows better clinical outcome for patients in CP-B, PS-1, recurrent HCC and with bilobar lesions. (Cardiovasc Intervent Radiol 33:41–52, 2010).

Based on these past evidences, Lipiodol-TACE and DEB-TACE may be indicated to the following conditions (IV). However, the farther clinical trials are required to obtain the exact answer.

Indication of Lipiodol TACE

- Hypervascular
- Less than 5 cm
- Superselective TACE if available

Indication of DEB-TACE

- Too many tumors for superselective TACE
- Not hypervascular
- Worse PS or liver function (PS-1, CP-B)

Speaker's Curriculum Vitae

Name Shiro Miyayama
Position Chief Director
Institution Department of Diagnostic
Radiology, Fukuiken Saiseikai
Hospital, Fukui, Japan



Shiro Miyayama graduated from Tottori University School of Medicine, Yonago, Japan at 1986 and started his residency in Radiology at Department of Radiology Kanazawa University Hospital, Kanazawa, Japan. He moved to Fukuiken Saiseikai Hospital, Fukui, Japan in 1995 and has been Chief Director of Department of Diagnostic Radiology since 2009.

Dr. Miyayama has published 58 scientific papers as the first author in the major peer-reviewed English journals. He is an Assistant Editor of Japanese Journal of Radiology and Editorial Board of Cardiovascular Interventional Radiology.

Research Interest: Abdominal Imaging, Interventional Radiology.

Satellite6-3

Role of Superselective Lipiodol TACE

Shiro Miyayama

Department of Diagnostic Radiology, Fukuiken Saiseikai Hospital, Fukui, Japan

The prognosis of patients with inoperable HCC has improved with advances in therapeutic options such as local ablation therapies in addition to TACE. In the majority of patients with HCC initially treated by some therapeutic options other than TACE, TACE may be required during the subsequent course due to the high incidence of tumor recurrence. Therefore, TACE still plays an important part in the treatment of inoperable HCC.

With advances in catheter-guidewire technology, it has become possible to introduce a microcatheter into a tumor-feeding branch. When Lipiodol is injected at a distal level of the hepatic artery, some Lipiodol flows into the portal veins through the peribiliary plexus and tumor drainage. Lipiodol can block the portal blood flow temporarily, followed by gelatin sponge slurry to completely obstruct the tumor-feeding branch. This leads not only to complete necrosis of the tumor including the well-differentiated tumor portion but also to massive peritumoral necrosis. Furthermore, superselective cTACE can treat not only the tumor but also the tumor drainage area by overflowed Lipiodol, where HCC cells spread mainly via the portal system and form intrahepatic satellite lesions. Therefore, this technique is an alternative option for small tumors and may contribute to the prevention of tumor spread via the portal system or control preexisting microsatellite lesions, and may reduce the incidence of locoregional tumor recurrence.

Additionally, superselective technique can also reduce the liver damage by TACE. In cases of large tumors, stepwise superselective cTACE should be recommended to avoid acute tumor-lysis syndrome. This technique can also bring an excellent result in localized large HCC. We believe that superselective cTACE plays an important role in the treatment of small and/or localized HCC lesions.

Speaker's Curriculum Vitae

Name Kenji Ikeda, MD, PhD
Position Director
Institution Department of Hepatology,
Toranomon Hospital, Tokyo, Japan



Born in Kyoto city (Japan) in 1953.

Career:

1972–1978 Gifu University, School of Medicine
1978 Resident, Department of Internal Medicine, Toranomon Hospital,
Tokyo.
1984 Physician, Department of Gastroenterology, Toranomon Hospital
1992 Head Physician, Department of Gastroenterology, Toranomon
Hospital
2006 Director, Department of Hepatology, Toranomon Hospital

Fields of Study:

Treatment of viral hepatitis.
Pathogenesis of hepatocellular carcinogenesis.
Prevention of liver cancer.
Medical treatment of hepatocellular carcinoma.

Satellite6-4

Balloon-Occluded TACE

Kenji Ikeda

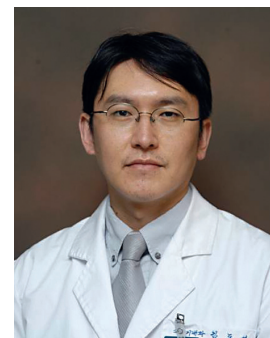
Department of Hepatology, Toranomon Hospital, Tokyo, Japan

Balloon occlusion of peripheral part of hepatic arteries induces an alteration of hemodynamics of hepatocellular carcinoma (HCC) and its surrounding liver tissue. We can inject lipiodol and anti-tumor agents more selectively for HCC through a micro-balloon catheter. Among various manners of transcatheter arterial chemoembolization (TACE), including conventional TACE and embolization of microspheres, balloon-occluded TACE is one of the most effective ways of treatment for multiple HCCs hard to treat with surgery or radiofrequency ablation.

We should realize the advantages of the balloon-occlusion technique and elucidate the effective utilization of the procedure.

Speaker's Curriculum Vitae

Name Do Young Kim, MD, PhD
Institution Associate Professor
Institution Department of Internal Medicine,
Yonsei University College of
Medicine, Seoul, Republic of Korea



Do Young Kim is now an associate professor of Internal Medicine at Yonsei University College of Medicine, Seoul, Korea, and a hepatologist in the Severance Hospital where he has been a faculty member since 2007. He graduated Yonsei University at 1996, and completed training course in Severance Hospital from 1996 to 2001. He studied proteomics and microRNA in hepatocellular carcinoma (HCC) at Fred Hutchinson Cancer Research Center as a research associate between 2011 and 2012.

He has been a vice secretary general in Korean Association of Gastroenterology from 2007 to 2009, and in Korean Liver Cancer Study Group between 2009 and 2010. Now he is a treasurer of the KASL. He is also a member of Korean Association for the Study of Liver Disease (KASL) and International Liver Cancer Association (ILCA).

His main research interest is biomarker including AFP-L3 for HCC and treatment of advanced HCC. He is one of the investigators in several clinical trials related to molecular target drugs for HCC. He published approximately 150 international original articles, and is an academic editor of PLoS ONE, Yonsei Medical Journal and World Journal of Hepatology. He also acts as a reviewer of Liver International, Gut and Liver, Molecular and Clinical Hepatology, and Journal of Korean Medical Sciences.

Satellite6-5

Role of Yttrium-90 Radioembolization in the Management of Hepatocellular Carcinoma

Do Young Kim

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Yttrium-90 radioembolization has emerged as a novel therapy for hepatocellular carcinoma (HCC) of intermediate or advanced stage. Yttrium-90 has characteristics of short half-life and tissue penetration depth. Potent anti-cancer effect by this isotope enables to kill the tumor for 6 months after administration. Although transarterial chemoembolization (TACE) is the standard modality for multinodular HCC without vascular invasion, big size or numerous nodules does not allow enough treatment effect of TACE. Post-embolization syndrome resulting poor quality of life, liver dysfunction and hepatic arterial damage are other pitfalls of TACE. In several studies, radioembolization showed survival comparable to TACE, shorter hospital stay and less treatment sessions. In advanced HCC with portal vein invasion, radioembolization demonstrated similar or better survival compared with sorafenib. The atrophy of lobe treated by radioembolization and hypertrophy in the contralateral lobe can be called radiation lobectomy, which makes it possible to perform a following curative therapy. The role of radioembolization in unresectable HCC in terms of downstaging or bridge to transplantation needs to be further studied. Radioembolization is contraindicated in HCC patients with main portal vein occlusion and with poor liver function. The International guidelines for HCC have some limitations and thus rooms for radioembolization to be incorporated.

Oral and Poster Sessions

O1-1

A Novel Strategy for Comprehensive Isolation of Fully Human Antibodies Against Unknown Target Molecules on Cell Surface of Hepatocellular Carcinoma Using Antibody Phage-Display Libraries

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Background: Hepatocellular carcinoma (HCC) is well known for its diversity that is a major therapeutic issue. Although antibody (Ab) should be the most promising candidate, non-human nature and lack of known target molecules has been main obstacles. To overcome the difficulties, we established a novel strategy for comprehensive isolation of fully human monoclonal antibodies (mAbs) against unknown target molecules on cancer cell surface using Ab phage-display libraries.

Methods: We developed a novel screening method termed ICOS that enabled isolation of mAbs against unknown molecules bound on cell surface. Two types of Ab phage-display libraries were screened using 7 cell lines and fresh specimens. Thereafter, the target molecules were identified with the mass-spectrometer. Clones with unique sequences were picked up and specific clones were selected by immunostaining. Antitumor activity was evaluated in vitro and in vivo. Correlation between the immunostaining patterns and clinicopathological features of 21 resected cases was investigated.

Results: We isolated 1,070 mAbs with unique sequences and found 158 mAbs that gave tumor-specific immunostaining patterns. Nineteen target molecules were identified including IGSF4, CD46, CD54, CD166, CD239, EGFR, PTP_LAR, CD315, Tfr1, CD147, CD298, CD44, EpCAM and CK7. Many mAbs showed strong antitumor activity, whereas those against different epitopes on the same molecule showed different antitumor activity. Although the immunostaining patterns were completely different, each case had own sets of specific mAbs. Some clinicopathological features showed correlation with immunostaining patterns.

Conclusion: A large number of tumor-specific fully human mAbs against HCC would reveal precise molecular basis and provide a promising personalized approach.

O1-2

Morphometric and Immunohistochemical Study of Cholangiolocellular Carcinoma: Focusing on Stem Cell Markers

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Background: The origin of cholangiolocellular carcinoma (CoCC) is still controversial. It has been speculated as malignant counterpart of cholangiole which has stem cell character. However, its stem cell feature has not yet been clearly proved so far. Furthermore, CoCC has also been speculated as interlobular duct (ILD) origin. Our former study showed CoCC resembled ILD more than cholangiole both in morphometric and immunohistochemical studies. More studies are necessary to clarify whether CoCC truly has stem cell character. To solve this problem, immunohistochemical features of CoCC should be examined using various stem cell markers.

Methods: Material; Cancerous ducts: Fifteen CoCC lesions from 13 resected and 2 autopsied cases. Non-neoplastic ducts: Twenty three specimens of non-cancerous areas of 23 resected liver tumors. From these specimens, CoCC ducts (n = 1506),

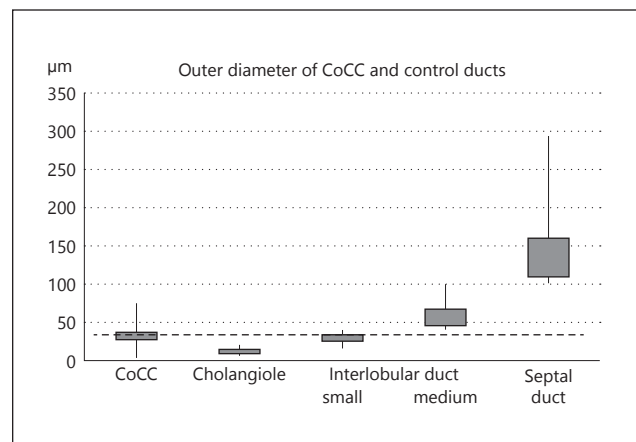


Fig. 1. (for Abstract O1-2).

cholangioles (n = 398), interlobular ducts of small size (ILD-S) (n = 344), interlobular ducts of medium size (ILD-M) (n = 209) and septal ducts (n = 82) were randomly selected. Morphometry; The outer and inner diameters of these ducts were measured using virtual slide system. Immunohistochemistry; Various stem cell markers, CD90, CD133, CD56, DLK1, EpCAM, SOX9, SALL4 were used. The positive ratio of the each antibody was examined in CoCC and various control ducts.

Results: Morphometry; Both mean values of the outer and inner diameters of CoCC (32.4 μ m, 11.3 μ m) were far larger than those of cholangioles (11.4 μ m, 0.1 μ m), and showed intermediate values between those of ILD-S (28.5 μ m, 6.2 μ m) and ILD-M (57.2 μ m, 17.9 μ m). Immunohistochemistry; CD90 and SALL4 were negative in all of CoCC and non-cancerous control ducts. Positive ratio of each antibody in CoCC, cholangiole, ILD-S, ILD-M was as follows: CD133 (20%, 1.0%, 15.7%, 5.7%), CD56 (39.1%, 9.6%, 5.0%, 5.7%), EpCAM (40.0%, 44.5%, 75.2%, 79.4%), DLK1 (5.1%, 0%, 0%, 0%). Although CD133, CD56 and EpCAM were positive in CoCC and cholangiole, they were also positive in ILD-S and ILD-M. DLK1 was positive only in CoCC. However, it was negative in any control ducts. These results could not prove stem cell char-

acter of CoCC. Moreover, the results showed low specificity of these so-called 'stem cell markers'.

Conclusion: Stem cell character of CoCC was not proved. As to the origin of CoCC, possibility of interlobular duct should also be discussed in the future.

O1-3

The Diagnostic and Prognostic Value of MRP8 and MRP14 in Intrahepatic Cholangiocarcinoma

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Background: To investigate diagnostic and prognostic values of myeloid-related protein 8 (MRP8) and MRP14 for intrahepatic cholangiocarcinoma (ICC) and benign bile duct diseases. MRP8 and MRP14 are expressed in several kinds of

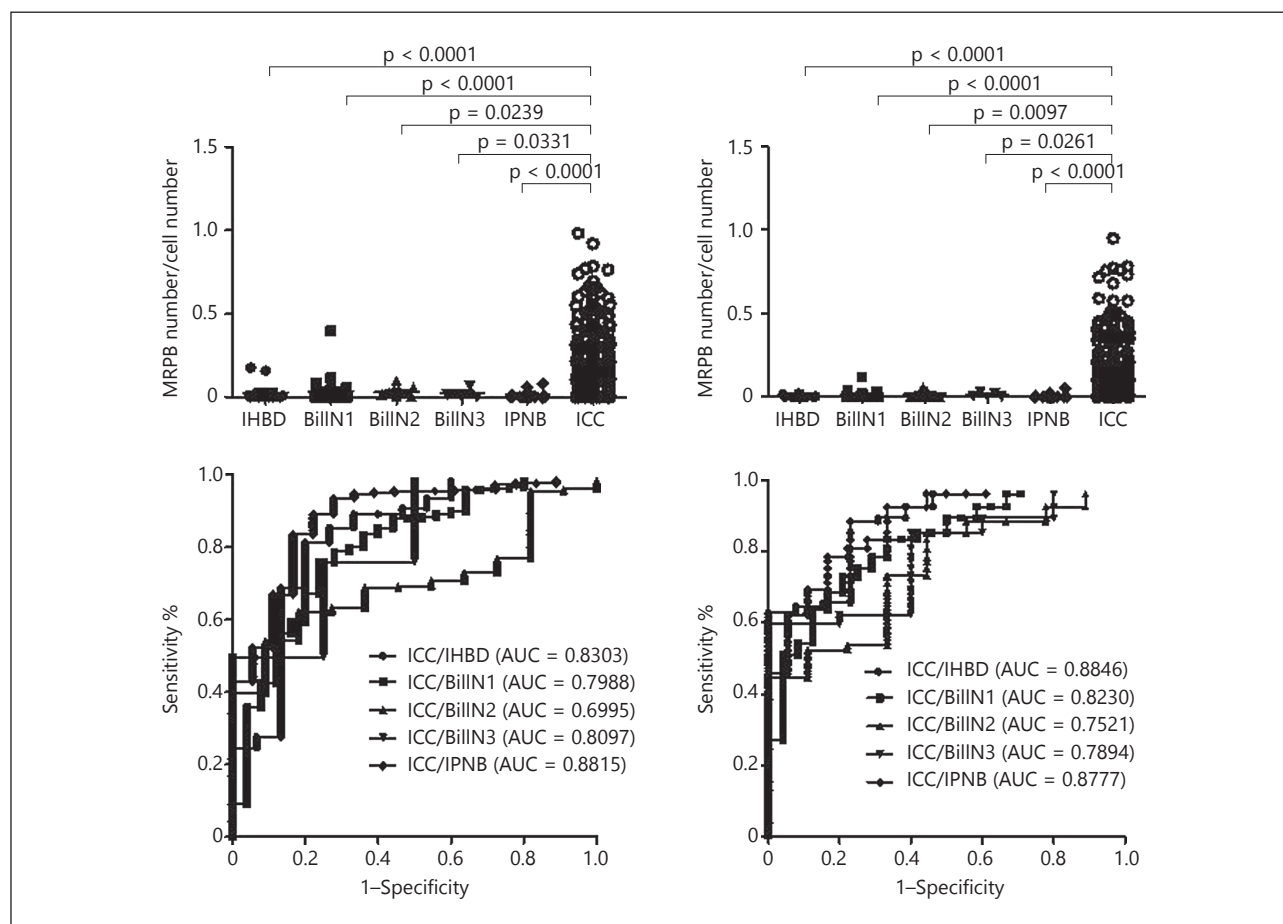


Fig. 1. MRP8 and MRP14 expression levels (MRP positive cells/bile duct derived cells) were significantly increased in ICC tissues than other nonmalignant tissues including IHBD, BiILN1, BiILN2, BiILN3, IPNB (all of these p value were <0.05) (for Abstract O1-3).

benign neoplasia and malignant tumor, however little is known about the pathoclinical significance of MRP8 and MRP14 in ICC, biliary intraepithelial neoplasia (BilIN), intra-ductal papillary neoplasm of bile duct (IPNB), and inflammatory hepatic biliary ducts epithelium (IHBD).

Methods: We examined MRP8 and MRP14 expression levels by immunohistochemistry in IHBD (n = 18), BilIN (BilIN1 = 29, BilIN2 = 10, BilIN3 = 5), IPNB (n = 18) and ICC (n = 429). The differential diagnostic and prognosis value were also evaluated.

Results: It's was showed that MRP8 and MRP14 expression levels (MRP positive cells/bile duct derived cells) were significantly increased in ICC tissues than other nonmalignant tissues including IHBD, BilIN1, BilIN2, BilIN3, IPNB (all of these p value were <0.05) (Figure 1). In addition, overexpression levels of MRP8 and MRP14 were correlated with overall survival (OS) and time to recurrence (TTR) of patient by univariate analysis and MRP8/MRP14 combination was independent prognostic factor for OS and TTR.

Conclusions: Our results suggest that MRP8 and MRP14 can identify benign bile duct diseases from ICC, and high expression level of MRP8 and MRP14 suggest poor prognosis of patient after curative resection.

O1-4

Clinicopathological Characteristics of Scirrhous Hepatocellular Carcinoma

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Background: Scirrhous hepatocellular carcinoma (sHCC) is a rare variant of primary liver cancer which is characterized by its rich fibrous stroma. Little is known about the clinicopathological features of sHCC. The aim of this study is to analyze the histological features of sHCC in detail and to investigate the clinicopathological differences between sHCC and ordinary HCC.

Methods: Sixty two samples were selected as sHCC whose tumor cut surface had irregular border, no bulge, and lacking fibrous capsule formation. Thirty four cases of ordinary HCC were selected as a control according to WHO criteria of nodular type HCC. Area ratio of fibrous components, age, sex, tumor size (average, mean), viral infection (HBsAg,

HCVAb), background liver inflammation, tumor differentiation, intrahepatic metastasis, portal invasion, venous invasion, bile duct invasion, serum alpha-fetoprotein level, overall survival rate and recurrence-free survival rate were examined in comparison with ordinary HCC.

Results: All sHCC samples contained fibrous components in more than 50% of the largest tumor area (51–100%), but ordinary HCC contained less (0–41%). Fibrous patterns in sHCC were histologically divided into 'septal' and 'mesh' components among 'non-scirrhous' components. Non-B, non-C cases were high compared with ordinary HCC (54.8% and 30.4%, p = 0.003). Particularly, HCVAb positive cases were significantly low (21.0% and 49.4%, p = 0.001), while HBsAg positive cases showed no difference (25.8% and 21.5%, p = 0.551). Bile duct invasion was occasionally detected in sHCC in contrast with the low frequency in classical HCC (16.1% and 1.3%, p = 0.001). Better recurrence-free survival rate was seen in sHCC (p = 0.015), however no significant difference was seen in overall survival rate. sHCC with septal components were larger in size than sHCC only with mesh components (p = 0.025). There was no significant difference between sHCC and ordinary HCC in other factors.

Conclusion: In contrast to ordinary HCC, sHCC could be histologically defined by expressing 50% or more fibrous components. Its clinicopathological features were also distinctive. These findings suggest that sHCC might have different carcinogenic process from ordinary HCC, and we consider sHCC as a distinct subtype of HCC.

O1-5

Clinicopathological Study of Intrahepatic Mucinous Carcinoma

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Objective: Primary intrahepatic cholangiocarcinoma belongs to a rare disease group, accounting for 5% to 15% of all hepatic tumors; adenocarcinoma with rich stroma has been known to represent a typical histological subtype. Intrahepatic mucinous carcinoma (IMC) is a rare histological subtype, most frequently presenting with intrabiliary growth. It has been reported that IMC has been associated with intestinal mucin phenotype, which is MUC2 expression and MUC1 non-expression, is histologically different from typical intrahepatic cholangiocarcinoma. However, few studies have investigated IMC. In this study, we investigated the pathological features of IMC in 3 cases.

Material and Methods: We analyzed the histopathological characteristics, and MUC1 (biliary type) and MUC2 (intestinal type) expression of IMC using 2,462 cases of

primary hepatic carcinoma resected in our hospital between 1985 and February 2015.

Results: The incidence of IMC was 0.1% (3 of 2,462 cases). Two tumors were localized in the hepatic hilus (hilar type) and one tumor was in the peripheral region (peripheral type). Macroscopically, the 2 cases of hilar type showed mass formation with intrabiliary growth, while 1 case of peripheral type showed well-circumscribed mass formation alone. Microscopically, all cases were mucinous carcinoma with mucous lake. Peripheral type showed pure mucinous carcinoma features, however, the 2 cases of hilar type contained areas of tubular adenocarcinoma and intraductal papillary neoplasm of the bile duct (IPNB)-like component. There was transitional area among mucinous carcinoma, tubular adenocarcinoma and IPNB-like components. Immunohistochemical analysis revealed MUC1 expression in all cases, and MUC2 expression, which is often observed in IPNB, in 2 cases.

Conclusions: Our study suggested that (1) Intrahepatic mucinous carcinoma represents a rare histological subtype, (2) there were differences in histological findings between hilar and peripheral types, and (3) hilar type might be originated from IPNB.

O2-1

Early Perfusion Changes Measured by Dynamic Contrast-Enhanced MRI May Predict Survival in Patients with Advanced Hepatocellular Carcinoma

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Backgrounds: Dynamic contrast-enhanced MRI (DCE-MRI) can evaluate perfusion changes within tumors after treatment. This study evaluated the early changes of DCE-MRI parameters within one week after systemic therapy in patients with advanced hepatocellular carcinoma (HCC) and correlated these changes with survival outcome.

Methods: After institutional review board approval and informed consent were obtained, 89 patients with advanced HCC agreed to undergo DCE-MRI before and within one week (3–7 days) after treatment. Among these patients, 35 received Vandetanib (100 mg or 300 mg, group 1), 38 received sorafenib plus tegafur/uracil (group 2) and 16 received best supportive care (group 3). Three semiquantitative parameters (Peak, Slope and iAUC) by curve-analysis method and three quantitative parameters (Ktrans, Kep, Ve) by a single-input dual compartment model were calculated by placing an operator-

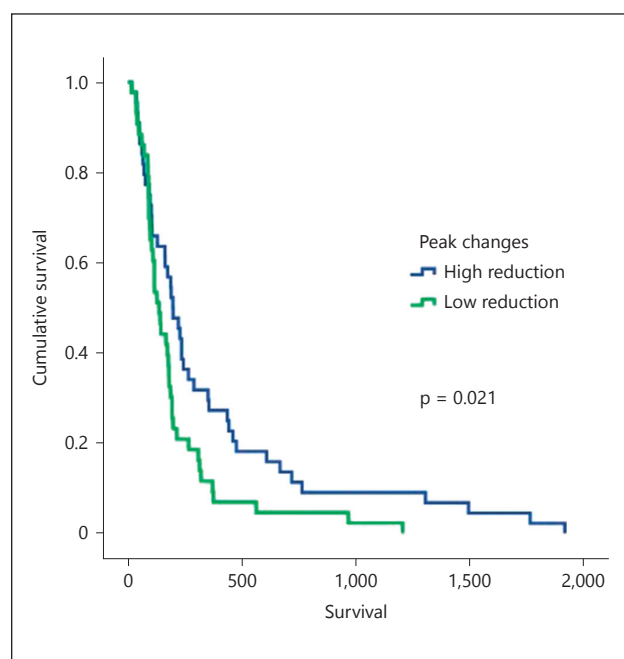


Fig. 1. (for Abstract O2-1).

defined region of interest in the largest area of the tumor. The relative changes $[(\text{Post} - \text{baseline})/\text{baseline}] \times 100\%$ of these six parameters before and after treatment were divided into high and low reduction groups by their median values. Overall survival (OS) were assessed with the Kaplan-Meier model, while differences between patient groups with high and low reductions were assessed by using the two-sided log-rank test.

Results: All patients died by December 2013 (median survival 174 days). Patients who received target/systemic treatments had longer OS than those with best supportive care (group 1 vs. 2, median survival 180 vs. 110 days, $P = 0.027$; group 2 vs. 3, median survival 193 vs. 110 days, $P = 0.016$), but no difference between two target/systemic treatment groups (group 1 vs. 2, median survival 180 vs. 193 days, $P = 0.82$). Among 6 DCE-MRI parameters, reductions in Peak, iAUC, and Ktrans, indicating decrease in tumor perfusion after treatment, were significantly correlated with one another (correlation coefficient: 0.379 for Peak vs. iAUC and 0.326 for Peak vs. Ktrans, respectively, $P < 0.01$ for both). Besides, patients with high Peak reduction after treatment had longer OS (median survival 197 vs. 137 days, $P = 0.021$) than those with low Peak reduction.

Conclusions: Early perfusion changes within one week after target/systemic treatment measured by DCE-MRI may help predict clinical outcome in advanced HCC patients.

O2-2

Imaging and Pathological Characteristics of Hepatocellular Carcinoma with β -Catenin Mutation

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Purpose: The purpose of this study is to identify the imaging features of HCC associated with β -catenin mutation and their relationship to pathological findings.

Materials and Methods: Surgically resected 138 HCCs were analyzed in this study. Immunohistochemical expression

of β -catenin and its transcriptional product glutamine synthetase (GS) were graded, and then classified into three groups: β -catenin(+)GS(+) group defined as HCC with β -catenin mutation, β -catenin(–)GS(+) group as intermediate type HCC and β -catenin(–)GS(–) group as HCC without β -catenin mutation. We compared these three groups with respect to the clinical, pathological and imaging findings of dynamic CT and gadoxetic acid enhanced MR imaging: T1 weighted image, T2 weighted image, diffusion weighted image (DWI) and hepatobiliary (HB) phase. We also evaluated the correlations between immunohistochemical expression of β -catenin, GS and OATP1B3 (uptake transporter of gadoxetic acid).

Results: HCC with β -catenin mutation (n = 27) showed a lower contrast noise ratio (CNR) on DWI (P = 0.02), higher apparent diffusion coefficient (ADC) value (P < 0.0001), higher CNR (P < 0.0001) and higher enhancement ratio on HB phase (P < 0.0001) than those of intermediate type HCC (n = 23) or HCC without β -catenin mutation (n = 84). Pathologically, HCC with β -catenin mutation frequently showed pseudoglandular proliferation and bile production with higher grade of differentiation (P < 0.05). There were significant positive correlations between expression of β -catenin, GS and OATP1B3 (P < 0.0001).

Conclusion: HCCs with β -catenin mutation showed higher grade of differentiation with frequent pseudoglandular pattern and bile production. Characteristic imaging findings such as high enhancement ratio on gadoxetic acid enhanced MR imaging and high ADC value on DWI are useful to diagnose this subtype of HCC.

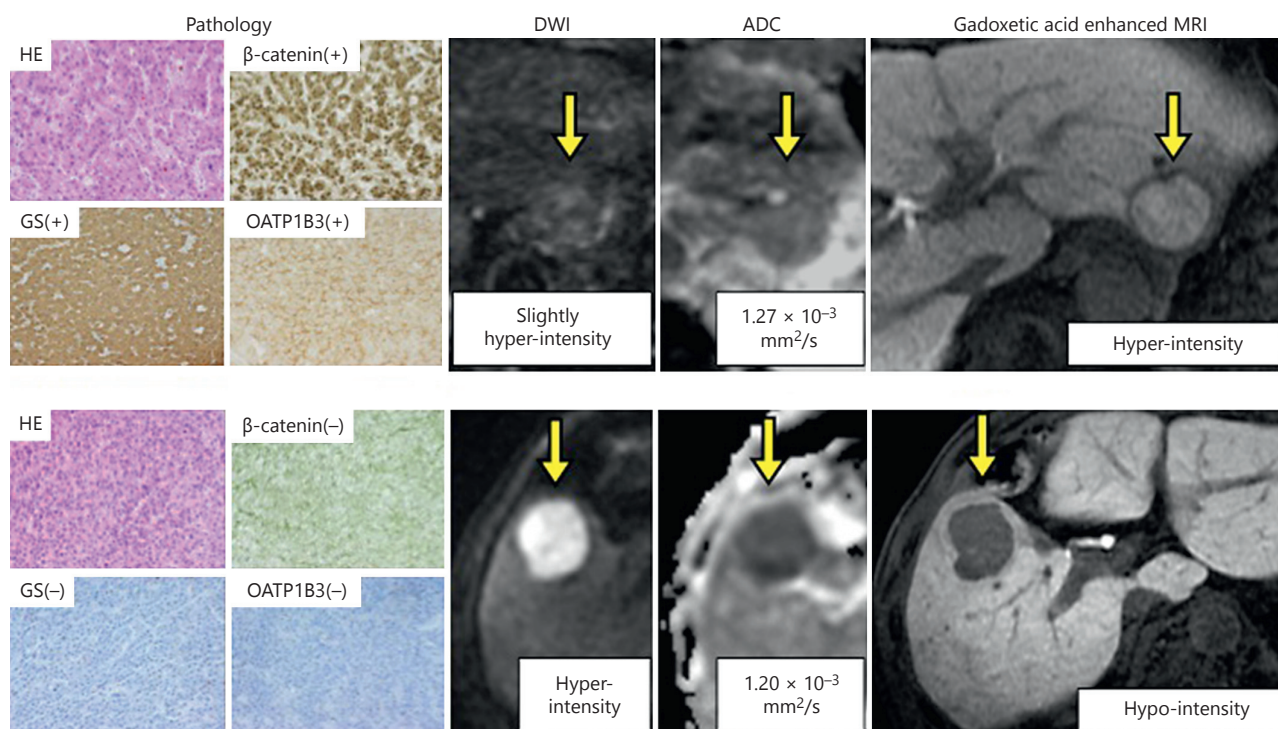


Fig. 1. HCC with (β -catenin mutation (above) and HCC without (β -catenin mutation (below) (for Abstract O2-2).

O2-3

Dynamic Contrast-Enhanced Magnetic Resonance Imaging with Gadoteric Acid for the Evaluation of Liver Parenchymal Changes in Hepatocellular Carcinoma

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Background & Aims: Radiofrequency ablation (RFA) is considered as a curative local therapy for early-stage hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE) is recommended as first line therapy with survival advantages in HCC patients with intermediate-stage disease. In general, RFA induces minimal damage to non-tumorous liver parenchyma. As contrast, TACE causes parenchymal injury in the embolized territory. This study evaluated liver parenchymal changes by using gadoteric acid-enhanced dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in patients with HCC after loco-regional therapy and correlated with the clinical liver function status.

Materials and Methods: DCE-MRI was performed in 7 HCC patients treated with RFA and 5 HCC patients treated with TACE at baseline and 3 days after treatment. Two DCE-MRI models were measured: (1) a dual-input single-compartment model to obtain arterial fraction (ART), arterial blood flow (Fa), portal blood flow (Fp), total blood flow (Ft), distribution volume (DV), and mean transit time (MTT); (2) a curve analysis method to obtain slope, area under curve (AUC), and time to peak (TTP). Biochemical data included serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels also obtained. Changes in the DCE-MRI parameters were analyzed and correlated with the clinical liver function status.

Results: After 3 days later of loco-regional treatment, the median ART (41.8% vs. 290.5%, $p = 0.05$), Fa (-0.2% vs. 398.3%, $p = 0.023$), Fp (37.4% vs. 30724.7%, $p = 0.009$), Ft (-13.6% vs. 1145.4%, $p = 0.010$), DV (-30.1% vs. 182.1%, $p = 0.015$) and TTP (-1.9% vs. -14.0%, $p = 0.001$) changes could significantly differentiate the patients treated with RFA from those treated with TACE.

Conclusions: Gadoteric acid-enhanced DCE-MRI parameters may be used to evaluate the early liver parenchymal changes and explain the liver function change in patients with HCC after loco-regional therapy.

O2-4

Phase I Dose-Escalation Study on Radiotherapy to Child-Pugh a Hepatocellular Carcinoma Patients-Predictive SUV on PET and Prognostic Serum Matrix Metalloproteinase-2

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Background: External radiotherapy (RT) has been controversial for patients with locally advanced hepatocellular carcinoma (HCC) unsuitable for curative therapies, mainly due to diverse patterns of failure. The optimal RT dose and effective biomarkers are imperative to guide treatment decision.

Methods: In this phase I study, HCC patients who had Child-Pugh A cirrhosis and unfit for curative therapies were enrolled. RT dose escalated from 42 Gy up to 63 Gy with the 7-Gy increase in 2 fractions (3.5 Gy per fraction) for a total of four levels. The study goals were to determine the maximally tolerated dose of RT, evaluate the disease outcomes, assess the impact of tumor standardized uptake value (SUV) from 18F-FDG PET/CT on treatment response monitoring, and collect blood samples for biomarker research. Fifty-five biomarkers were first screened using proximity ligation assay (PLA), an antibody-based method of protein detection. Biomarkers with PLA data significantly correlated with clinical outcome were verified by ELISA.

Results: A total of 16 patients were enrolled and no dose limiting toxicity was encountered in this trial. Only one patient developed grade 3 pneumonitis after RT which resolved after oral steroids. Among the 4 significant biomarkers (MMP-2, VEGFa, TGF- β , and MMP-9) by PLA screening, patients with local tumor control (LC) ≥ 6 months had significantly lower pre-RT MMP-2 level than patients with LC < 6 months (absolute concentration 259.7 ± 21.4 ng/ml vs. 360.3 ± 38.0 ng/ml, $p = 0.03$; log2 PLA units 9.1 ± 0.4 vs. 10.2 ± 0.3 , $p = 0.04$). Patients developing distant metastasis (DM) had a trend of higher post-RT SUV of irradiated liver tumor than patients without DM (4.1 ± 0.4 vs. 3.3 ± 0.2 , $p = 0.06$). In patients with pretreatment alpha-fetoprotein above normal range (AFP > 20 ng/ml), both the pre-SUV (8.8 ± 1.5 vs. 4.1 ± 0.5 , $p = 0.008$) and

post-SUV (4.4 ± 0.5 vs. 3.2 ± 0.3 , $p = 0.04$) were significantly higher in patients with DM than patients without DM.

Conclusions: In patients with Child-Pugh class A HCC, dose escalated up to 63 Gy in 18 fractions was well tolerated. MMP-2 is a prognostic serum biomarker for RT response. The high post-RT SUV of tumor is a predictor for metastases.

O3-1

Recurrent Feature After Radiofrequency Ablation Therapy for Hepatocellular Carcinoma – Risk of Increasing Malignant Behavior

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Background: Radiofrequency ablation (RFA) is a widely used therapy for hepatocellular carcinoma (HCC). However, several reports demonstrated the aggressive local recurrence after RFA, suggesting the induction of further malignant transformation of HCC.

Method: Eighty-eight patients with HCC who underwent hepatic resection were included in this study. Hepatectomy was indicated for local recurrence of HCC after RFA ($n = 10$, RFA group) and for the HCC without prior RFA ($n = 78$, non-RFA group). Clinicopathological data and patient's prognosis after hepatectomy were compared between the two groups. Expression levels of HIF-1, EpCAM, CD44, VEGF and EMT markers mRNA in the tumor tissues were examined. We also investigated miR-34a and miR-200c expressions in the two groups.

Results: RFA group showed higher frequency of portal vein invasion and less tumor differentiation compared with the non-RFA group ($p < 0.05$). Overall and disease-free survival rates in the RFA group were significantly worse than those in the non-RFA group ($p < 0.05$). HIF-1 and EpCAM mRNA expression levels in the RFA group were significantly higher than those in the non-RFA group ($p < 0.05$). The expressions of TGF- β , Twist and Snail-1 in RFA group were significantly higher than those in non-RFA group ($P < 0.05$), and Vimentin expression in RFA group tended to be higher than that in non-RFA group ($P = 0.07$). Regarding to miRNA, miR-200c and miR-34a expressions in RFA group were significantly lower than those in non-RFA group (miR-200c: $P = 0.04$, miR-34a: $P < 0.01$).

Conclusions: Recurrent HCC after RFA showed the highly malignant potential through the expressions of HIF-1, cancer stem cell and EMT markers.

O3-2

Long-Term Impact of Liver Function on Potentially Curative Therapy for Hepatocellular Carcinoma: Implications from Application of the ALBI Grade

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Objective: We sought to provide evidence that the recently described ALBI score [1] accurately reflects liver function in patients with hepatocellular carcinoma (HCC) and to use this score to examine the long term impact of liver dysfunction on survival of patients with early HCC where therapy with curative intent could be applied.

Patients and Methods: We accrued individual patient data from 1903 HCC patients with a variety of etiologies and from different geographic regions, all treated with curative intent. ALBI score was calculated based on the pretreatment laboratory data as $(\log_{10} \text{bilirubin } [\mu\text{mol/L}] \times 0.66) + (\text{albumin } [\text{g/L}] \times -0.085)$ and patients with ALBI score ≤ -2.60 were categorized as grade 1, < -2.60 and ≤ -1.39 as grade 2, and < -1.39 as grade 3. In a cohort of patients we examined the relation between indocyanine green (ICG) clearance and ALBI score. Patient survival rates after curative therapy were compared on the basis of ALBI grade.

Results: The ALBI score correlated well with ICG clearance. Among those undergoing surgical resection, patients with ALBI grade-1 (good liver function) survived approximately twice as long as those with ALBI grade-2 (less good liver function) although more than 90% of these patients were classified as Child-Pugh grade A. In the cohort receiving ablative therapies with curative intent, there was a similar difference in survival between ALBI grade-1 and -2 but the survival curves diverged significantly later. The ALBI grade accounted for the better survival of those with HBV-related HCC compared with HCV-related disease.

Conclusion: The ALBI score represents a simple approach to the assessment of liver function in patients with HCC. After potentially curative therapy, those with ALBI grade-1 survived twice as long as those with ALBI grade-2. Patients assessed as ALBI-2 may, where the option exists, be more suitable for liver transplantation or curative ablative therapies whereas ALBI-1 patients may be more suitable for hepatic resection.

Reference

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O3-3

Liver Stiffness Measurement for the Prediction of Posthepatectomy Liver Failure After Liver Resection for Hepatocellular Carcinoma

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Background: Posthepatectomy liver failure (PHLF) is a potentially fatal complication after liver resection for hepatocellular carcinoma (HCC) developed in the diseased liver. An accurate evaluation of preoperative liver function is essential to avoid PHLF, however, sometimes occurrence of PHLF is hard to predict preoperatively. Deteriorated liver function links to progression of liver fibrosis. Recently, liver stiffness (LS) measurement has been widely accepted as a noninvasive assessment for liver fibrosis, and it may be a useful tool for evaluating the preoperative liver function and for predicting PHLF.

Objective: To evaluate the usefulness of LS measurement in evaluating liver fibrosis and predicting PHLF for patients with HCC undergoing liver resection.

Methods: One hundred and seventy-seven patients with HCC undergoing liver resection between August 2011 and October 2014 were prospectively enrolled. Preoperative parameters such as platelet count, prothrombin time, serum bilirubin, and indocyanine green retention test were collected. LS was measured by acoustic radiation force impulse (ARFI) imaging and it was expressed as shear wave velocity (SWV) [m/s]. The remnant liver volume rate (Rem) was calculated by computed tomography volumetry. Liver fibrosis was defined by Metavir's fibrosis score. PHLF was diagnosed according to the International Study Group of Liver Surgery (ISGLS) definition and graded as A, B, or C. Receiver operating characteristics (ROC) analysis was performed to evaluate the predictive power of variables.

Results: The SWV elevated as liver fibrosis progressed; 1.36 ± 0.25 m/s in F0; 1.44 ± 0.40 m/s in F1; 1.60 ± 0.50 m/s in F2; 1.90 ± 0.73 m/s in F3; and 2.66 ± 0.88 m/s in F4. PHLF occurred in 38 patients (21.5%): Grade A, 17 patients (9.6%); Grade B, 15 patients (8.5%); and Grade C, 6 patients (3.4%). The area under ROC curve (AUROC) of SWV for predicting PHLF was: 0.67 for Grade $\geq$ A; 0.78 for Grade $\geq$ B; and 0.74 for Grade C; which was higher than any other preoperative factors for each grade. Multivariate logistic regression analysis (stepwise procedure using minimum AICc method) identified SWV and Rem as the significant factors associated with PHLF grade $\geq$ B, which requires medical intervention (SWV: odds ratio [OR]: 2.66, 95% confidence interval: 1.69 to 4.41, $p < 0.01$, Rem: OR: 0.47, 95% CI: 0.27 to 0.79, $p < 0.01$). The novel risk index based on the logistic model including SWV and Rem, SWV-Rem index ($1.25 \times \text{SWV}[\text{m/s}] - 3.97 \times \text{Rem}$), resulted in higher AUROC of 0.80 for the prediction of PHLF grade $\geq$ B.

Conclusions: LS measurement is useful for the prediction of PHLF for HCC patients undergoing liver resection.

O3-4

The Fate of Recurred Hepatocellular Carcinoma After Curative Primary Liver Resection; Are Still Pathologic Aggressiveness and Milan Criteria of the Primary HCC Important?

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Background: Liver resection offers the best outcome among the treatment options of hepatocellular carcinoma (HCC) in Korea in which the patient with HCC could not get a chance of deceased donor transplantation due to organ shortage. Even after surgical resection, the majority of patients will develop intrahepatic recurrence of HCC. However the fate and associated prognostic factors of the recurred tumor has not been well established although those would be treatment guideline including salvage liver transplantation after recurrence.

Methods: Between 2005 and 2011, a total of 959 patients who had intrahepatic recurrence after curative resection were reviewed.

Results: A total of 802 (83.6%) patients were male. The median duration between primary resection and recurrence was 11.0 (1~114) months. At primary resection, 579 (60.4%) patients had HCC within Milan's criteria and pre/post-operative AFP level more than >200 ng/ml showed in 723 (81.1%)/767 (85.7%) patients. On pathologic exam, microscopic vascular invasion was noted in 292 (30.4%) patients, major vessel involvement in 278 (29.0%) patients, the worst Edmondson-Stein grade $\geq$ III in 106 (11.1%) patients, and multi-nodular type in 190 (19.8%) patients. At the time of recurrence, 750 (81.8%) patients had HCC within Milan's criteria, AFP level >200 ng/ml showed in 169 (18.9%) patients, and the first treatment modality was TACE in 549 patients (57.2%). The 5-year disease free survival (DFS) rate after the 1st recurrence was 42.7%. In multivariate analysis, the factors associated with disease free survival after 1st recurrence were the worst Edmondson-Stein grade $\geq$ III, HCC beyond Milan criteria at the time of primary resection, and HCC beyond Milan criteria at the time of the 1st recurrence ($p < 0.05$). The 5-year DFS rates after the 1st recurrence of patients with at least one of these factors (37.5%) was poorer than those of the others without these risk factors (57.9%) ($p = 0.000$).

Conclusion: The pathologic aggressiveness of the primary tumor and the Milan criteria of the primary and the

secondary tumor were the important factors of DFS rates after the recurred HCC after primary resection. Those factors would be guideline of decision for treatment of recurred HCC after primary resection.

O4-1

Relationship Between Hepatocellular Carcinoma Development and Serum Viral Markers in Patients with Undetectable Serum HBV DNA Level While on Nucleos(t)ide Analogues

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Background & Aims: Hepatitis B surface antigen (HBsAg) and hepatitis B core-related antigen (HBcrAg) are risk factors for hepatocellular carcinoma (HCC) development. Linearized HBsAg kit (Lumipulse G HBsAg-Quant) is a novel assay allowing better quantification of HBsAg level. However, little is known whether they remain important for HCC development if there is profound suppression of viral replication by nucleos(t)ide analogues (NA).

Methods: Seventy-six HBV carriers who developed HCC despite undetectable serum HBV DNA (<20 IU/ml) after at least one-year NA therapy were compared with 152 matched controls who did not have HCC. Clinical and laboratory parameters were analysed in a cross-sectional manner.

Results: There was a significant difference in the median values of HBcrAg level between the HCC group and non-HCC group (10.2 and 1.7 kU/ml, respectively, $p = 0.005$), while there were no significant differences in HBsAg levels by conventional HBsAg kit and linearized HBsAg kit (Lumipulse G HBsAg-Quant). A cutoff value of HBcrAg level ≥ 7.8 kU/ml yielded an area under receiver operating curve (AUROC) of 0.61 (95% CI: 0.54–0.69) with a negative predictive value (NPV) of 77.0%. The odds ratio of HCC development was 3.27 (95% CI: 1.84–5.80). For the subgroup of non-cirrhotic patients, the median values of HBcrAg level of the HCC and non-HCC group were 10.2 and 1.0 kU/ml respectively ($p = 0.001$). A cutoff value of HBcrAg level ≥ 7.9 kU/ml yielded an AUROC of 0.70 (95% CI: 0.58–0.81) with a NPV of 80.6%. The odds ratio of HCC development was 5.95 (95% CI: 2.35–15.07).

Conclusion: A higher HBcrAg level (but not HBsAg level) was associated with an increased risk of HCC development in patients who achieved undetectable serum HBV DNA while on NA therapy.

O4-2

Estimation of Survival After Stopping Sorafenib in Patients with Advanced Hepatocellular Carcinoma: Development and Validation of the 'NEXT Score'

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Backgrounds/Aims: Although sorafenib (Nexavar[®]) is a standard treatment in patients with advanced hepatocellular carcinoma (HCC), little is known about the clinical disease course after halting sorafenib. Therefore, we investigated the predictors of survival after stopping sorafenib due to intolerance or progressive disease, and then developed and validated a novel survival prediction model named 'NEXT score' (Prediction of Survival after Stopping Nexavar Treatment) in patients with advanced HCC.

Methods: Clinical data on 409 patients with advanced HCC who discontinued sorafenib treatment due to intolerance or progressive disease between September 2008 and February 2015 were reviewed retrospectively. The study population was stratified into training ($n = 272$) and validation ($n = 137$) cohorts at a 2:1 ratio to develop and validate a survival prediction model.

Results: The mean age of the training cohort (225 men, 47 women) was 57 years. All baseline characteristics were statistically similar between the training and validation cohorts (all $P > 0.05$). The median survival of the training cohort was 6.4 (range 3.4–12.2) months. In the training cohort, six factors were identified as independent unfavorable predictors of survival on multivariate analysis (all $P < 0.05$): poor Eastern Cooperative Oncology Group (ECOG) performance status (≥ 2) (hazard ratio [HR] 1.543, 95% confidence interval [CI] 1.083–2.198); decreased liver function (Child-Pugh class B or C) (HR 1.891, 95% CI 1.332–2.685); high alanine aminotransferase level (ALT, >40 IU/L) (HR 1.359, 95% CI 1.010–1.829); low serum sodium level (≤ 135 mEq/L) (HR 1.792, 95% CI 1.292–2.486); high alpha-fetoprotein level (AFP, >400 ng/ml) (HR 2.225, 95% CI 1.637–3.025); and advanced tumor stage (Barcelona Clinic Liver Cancer [BCLC] stage C or D) (HR 1.893, 95% CI 1.258–2.847). Using the HR of each predictor, we allocated weighted values to each prognostic factor (2 points for ECOG ≥ 2 , Child-Pugh class B or C, serum sodium ≤ 135 mEq/L, AFP >400 ng/ml, and BCLC stage C or D and 1 point for ALT >40 IU/L) and established the NEXT score which ranged from 0 to 11 points. The areas under the receiver operating characteristic curve (AUROC) that predicted the 1-, 3-, and 6-month survival were 0.829 (95% CI, 0.774–0.883), 0.817 (0.767–0.866), and 0.782 (0.726–0.837),

respectively. In the validation cohort, the AUROC values of the NEXT score for 1-, 3-, and 6-month survival were 0.788, 0.748, and 0.700, respectively. When the training cohort was stratified into three risk groups according to the Next score (0-3 for low risk, 4-7 for intermediate risk, and 8-11 for high risk), survival differed significantly among the groups ($P < 0.05$, log-rank test). Similarly, stratification of the validation cohort into three risk groups using the NEXT score was also significant ($P < 0.05$, log-rank test).

Conclusions: Survival after stopping sorafenib was grave in patients with advanced HCC. Risk estimation using the new 'NEXT score' might be useful for predicting survival after stopping sorafenib treatment.

O4-3

Prediction of the Recurrence of Hepatocellular Carcinoma by Alpha-Fetoprotein After Radiofrequency Ablation

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Backgrounds: Hepatocellular carcinoma (HCC) is one of the most common cause of cancer-related deaths in the world. Surgical resection, liver transplantation, and radiofrequency ablation (RFA) were known as potentially curative treatment modalities. Recently, a spread of screening test achieved detection of HCC at early stage, and the cases who could receive local ablation therapies have increased. But a problem of recurrence still remains. HCC recurs at an annual rate of 20 percent even if radical treatment was performed for primary lesion. The high recurrence rate indicated that the liver was already in hyper-carcinogenic state at the time of HCC onset. Alpha-fetoprotein (AFP) is known as a tumor marker for HCC and cut-off levels were usually set at 20~200 ng/ml. AFP is also considered to be a marker for hyper-carcinogenic state. Recently, the risk for HCC in chronic hepatitis C patients with low AFP levels after sustained virological response was reported to be lower than that with high AFP. However, the cut-off levels were set at very low (5~10 ng/ml) in the reports that examined the hyper-carcinogenic state with AFP. In this study, we analyzed the risk factors of HCC recurrence after curative RFA and tried to elucidate the importance of AFP as a marker for hyper-carcinogenic state in patients with HCC.

Methods: Between 2001 and 2013, 1065 newly developed HCC patients were admitted in our hospital. In this study, 357 patients who underwent RFA for primary HCC (≤ 3 cm, ≤ 3 tumors) were enrolled. We analyzed the correlation between 17 clinical parameters including AFP after RFA

and the HCC recurrence by Cox-proportional Hazard model, retrospectively.

Results: Among 357 patients, 222 were men (62.2%) and a mean age was 70 y.o. Thirty nine patients had HBV infection, 285 had HCV, 4 had both HBV and HCV, and 29 had no hepatitis virus infection. Most of the patients ($n = 300$, 84.0%) were classified into Child-Pugh A. Recurrence was observed in 236 patients during a mean observation period of 54.3 months. Univariate analysis showed that male, low albumin and platelet count, high aspartate aminotransferase (AST, >40 IU/L), AFP (>10 mg/ml) and des- γ -carboxyprothrombin (DCP >40 mAU/ml), large tumor (>2 cm), and multiple tumors were significantly correlated with high HCC recurrence rate. Multivariate analysis with the factors revealed that multiple tumors (HR = 1.70, $p < 0.001$), high AFP (>10 ng/ml, HR = 1.45, $p < 0.001$) and high DCP (>40 mAU/ml, HR = 1.52, $p < 0.005$) were significant risk factors for recurrence. Same relationship was observed even if the cut-off level of AFP was set lower (5 ng/ml). The risk of recurrence increased linearly according to the increase of AFP level after RFA. In patients without recurrence for 3 years, 5 years and 7 years after RFA, the minimum levels of AFP after RFA was ≤ 268 , ≤ 23.0 and ≤ 11.2 ng/ml, respectively. The results indicated that the low AFP level was necessary to achieve long recurrent-free survival after RFA. Furthermore, if the AFP levels after RFA was normalized even though AFP levels before RFA was high, the rate of recurrence was as low as that in the patients with normal AFP levels before RFA.

Conclusions: AFP levels after curative RFA could predict HCC recurrence, indicating that AFP is considered to be a marker for hyper-carcinogenic state even in patients with HCC.

O4-4

A Prognostic Scoring System for Patients with Multiple Hepatocellular Carcinomas Treated by Hepatectomy

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Background: The selection criteria of hepatectomy for patients with multiple hepatocellular carcinomas (HCCs) remain controversial.

Methods: A scoring system based on preoperative data and independent predictors of overall survival (OS) was developed in a primary cohort of 510 patients who underwent hepatectomy for multiple HCCs from 1998 to 2006, and vali-

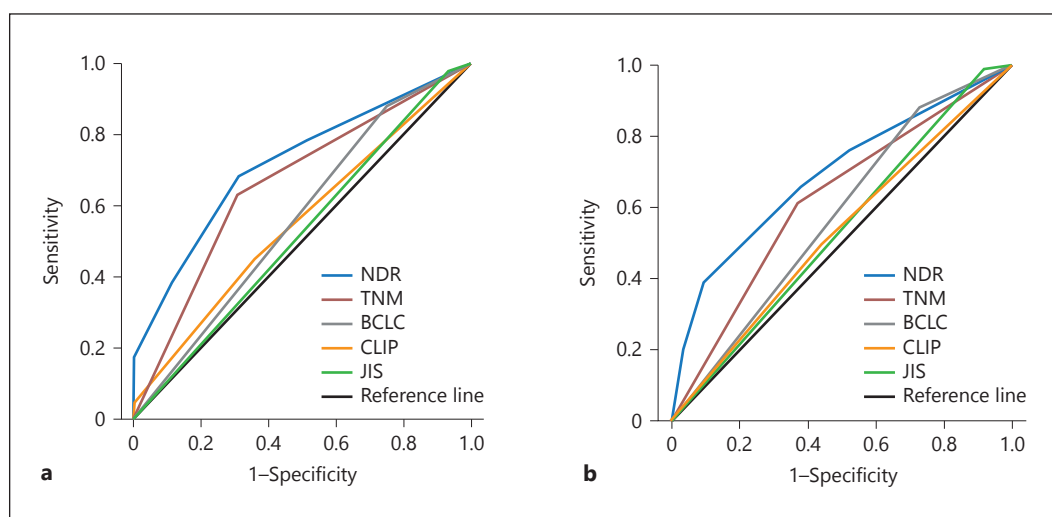


Fig. 1. (for Abstract O4-4).

dated in 177 patients who were operated from 2006 to 2009 at the Eastern Hepatobiliary Surgery Hospital.

Results: In the NDR scoring system, tumor number (N) >3, total tumor diameter (D) >8 cm, and a ratio of largest/smallest diameter (R) >6 were independent predictors of OS. Its predictive accuracy as determined by the area under the curve (AUC 0.718) was larger than the four conventional staging systems (0.524–0.662). It stratified postoperative OS into five levels (0–4 score). The 5-year OS rate of patients with a NDR score 0–2 was 46.5% versus 13.9% in those >2 ($P < 0.001$). Patients with a score 0–2 therefore were recommended for hepatectomy. The feasibility of this NDR score 0–2 was compared with the previously reported criteria. If the two more stringent inclusion criteria were adopted, 45.5–75.7% of patients with a NDR score 0–2 would be excluded, but their 5-year OS rates were comparable to those within the criteria (44.7% vs. 52.1%, $P = 0.083$; 46.6% vs. 46.3%, $P = 0.674$). If the less stringent criteria were used, an additional 25.9% of patients received hepatectomy, but their 5-year OS rate was 13.9%.

Conclusions. The NDR scoring system was more accurate in selecting patients with multiple HCCs for hepatectomy.

O4-5

Up-to-Seven Criteria Depicts the Superior Overall Survival After Conventional TACE Than Those Beyond Up-to-Seven in BCLC Stage B Patients with HCC

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Background: Four substages of BCLC intermediated hepatocellular carcinoma (HCC), based on up-to-seven criteria and Child-Pugh score were proposed. The patients with HCC in BCLC stage B should be treated by TACE according to AASLD and EASL guidelines.

Methods: The purpose of this study is to validate and to modify this proposal. Between April 1996 and March 2014, newly diagnosed intermediate HCC patients were treated by conventional TACE with lipiodol and gelatin sponge in combination with epirubicin. Patients were stratified into four (B1–B4) subgroups and followed up until death or March 2014. Patients' survivals and discriminatory ability of substaging system were compared. Three-hundred and ninety three patients were enrolled and those with single nodule smaller than 5 cm and 2 to 3 nodules ≤ 3 cm were excluded from the analysis.

Results: One, three and five year survival rate in BCLC subgroup B1 and B2 was 90.8%, 83.2% and 71.8% in B1 and 60.9%, 34.7% and 16.3% in B2, respectively, however there was no significant difference between the two groups. After

removing the patients with Child-Pugh point 7 from group B1, OS of the patients within up-to-seven criteria showed significantly better OS than those with outside up-to-seven criteria. If down staging by surgical resection or radiofrequency ablation was carried out after cTACE, OS could significantly improve than those without down staging ($p < 0.001$).

Conclusion: From these results, BCLC substages, especially up-to-seven criteria were clinically useful in predicting survival after cTACE but it should be revised to remove Child-Pugh point 7 from B1.

05-1

High Intensity Focused Ultrasound Ablation Plus TACE Versus TACE Alone for Unresectable HCC-A Case Matched Comparative Study in a Single Institute

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Background: High-intensity focused ultrasound (HIFU) ablation is a non-invasive treatment for unresectable HCC but long term survival analysis is lacking. In this study we aim to analyse the outcome of patients receiving this treatment compared to TACE.

Methods: From Oct 2003 to Sept 2010, 113 patients received HIFU as a treatment of HCC in Department of Surgery Queen Mary Hospital. Patients with residual tumour after ablation were treated with TACE. 26 patients had an HCC larger than 3 cm. 52 patients with matched tumour characteristic receiving TACE as primary treatment were selected for comparison. Short term outcome and long term survival outcome were analysed.

Results: In the HIFU group ($n = 26$) 46 tumours were ablated. The median age of the patients was 69 (range 49 years-84 years). The median tumour size was 4.2 cm (range 3–8 cm). In the TACE group ($n = 54$), the median age for the patients was 67 (range 44 years-84 years). The median tumour size was 4.8 cm (range 3–8 cm). There was no hospital mortality in both groups. In the HIFU group, the complete tumour response (CR), partial tumour response (PR), stable disease (SD) and progressive disease (PD) rate was 50%, 7.7%, 25.6% and 7.7% respectively versus 0%, 21.2%, 63.5% and 15.4% patients had progressive respectively in TACE group according to mRECIST criteria. ($p < 0.0001$) The 1-year, 3 year and 5-year survival was 84.6%, 49.2% and 32.3% respectively in the HIFU group versus 69.2%, 29.8% and 2.3% respectively in the TACE group. ($p = 0.001$)

Conclusion: HIFU ablation is a safe and effective method for unresectable HCC. A survival benefit is observed over TACE alone.

05-2

Survival After Intra-Arterial Treatment of Hepatocellular Carcinoma: Impact of Liver Dysfunction and Comparison with a Statistically-Modelled ('Virtual') Sorafenib Control Group: An East/West Collaborative Project

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Background: TransArterial Chemo-Embolisation (TACE) is recommended for patients with BCLC intermediate stage HCC (stage B) particularly in patients with excellent underlying liver function and minimal symptoms. When portal vein invasion (PVI) is apparent or there are extra-hepatic metastases, the systemic targeted agent Sorafenib is recommended, although TACE has not been compared directly ('head to head') to Sorafenib and, in practice, TACE is often instituted even in the presence of PVI. A recently developed measure of liver function (the ALBI grade) now permits detailed assessment of the impact of liver function on survival (1).

Methods: We accrued patient level data from a total of 2454 patients undergoing TACE – China ($n = 242$), Japan ($n = 655$), Europe (UK, Germany and Spain combined, $n = 559$) and Egypt ($n = 998$). Overall, 59% had Child-Pugh grade 'A' and 17%, PVI. Liver function was graded according to the ALBI grade. A statistical model for survival after TACE was built on a randomly selected half of a combined group of 1214 Japanese and European patients, $n = 602$ (323 Japanese and 279 European) and then validated on the remaining 612 patients (332 Japanese and 280 European). The TACE model was also validated on an independent cohort from Egypt ($n = 998$). Using a randomly selected half of patients accrued from Sorafenib control arms of two large international clinical trials ($n = 1130$) (2,3), we built a further model for survival after Sorafenib treatment, based on baseline clinical features. The

model was then validated on the remaining half of the cohort. The Sorafenib model was also applied on Egyptian patients undergoing TACE in order to predict their survival had they received Sorafenib.

Results: Our TACE model accurately predicted survival in the second half validation set (actual median survival = 20.4 months, predicted = 20.7 months) as well as in the Egyptian cohort (actual median survival = 18 months, predicted = 20 months). One year survival was 65.7% and 71.3% for actual and predicted respectively. Classification of patients according to their ALBI grade resulted in clear, non-overlapping survival curves in all cohorts. Our Sorafenib model accurately predicted survival in the validation set (actual median survival at 9.7 months whereas model predicted at 9.9). It also suggested that survival would be worse in the TACE patients had they received Sorafenib as a whole group (Sorafenib predicted = 12 months, TACE actual = 18 months), and in each of the three ALBI grades: ALBI 1 (Sorafenib predicted = 19 months, TACE actual = 30 months), ALBI 2 (Sorafenib predicted = 12 months, TACE actual = 18 months) and ALBI 3 (Sorafenib predicted = 5.5 months, TACE actual = 12 months).

Conclusions: ALBI categorised patients receiving TACE into three clear prognostic groups. Our TACE and Sorafenib models accurately predict survival after TACE and Sorafenib respectively on the basis of baseline clinical and laboratory features. Our virtual trial suggests that survival after TACE would compare favourably with Sorafenib overall and in individual ALBI grades.

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O5-3

Translational Research of Boron Neutron Capture Therapy for Primary Hepatocellular Carcinoma with Intra-Arterial Injection of Boron Entrapped WOW Emulsion

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Background: Tumour cell destruction in boron neutron-capture therapy (BNCT) is due to the nuclear reaction between ¹⁰B and thermal neutrons. For effective BNCT, it is necessary to accumulate ¹⁰B atoms in the tumour cells without affecting adjacent healthy cells. Applications of BNCT has been increased clinically in patients with a lot of cancers in hole body. The main two ¹⁰Boron compounds (¹⁰BSH: sodium mercapto-undecahydro-dodecaborate, ¹⁰BPA: ¹⁰B-p borono-phenylalanine) are used to clinical trials. Water-in-oil-in-water (WOW) emulsion has been used as the carrier of anti-cancer agents in intra-arterial injections for the treatments of hepatocellular carcinoma (HCC).

Methods: We prepared ¹⁰BSH containing WOW emulsion using a double emulsification technique with iodized poppy-seed oil (IPSO), ¹⁰BSH, and surfactant. WOW emulsion was

administrated with intra-arterial injections via the hepatic artery propria and compared the biodistributions with ^{10}B -IPSO mix conventional emulsion, and performed BNCT in a VX-2 rabbit hepatic tumour model.

Results 1: The ^{10}B concentrations in VX-2 tumour cells on delivery with WOW emulsion were superior to those using conventional IPSO mix emulsion. Electron microscopy images of the WOW emulsion showed the accumulation of fat droplets of WOW emulsion in the tumour cells, but there was no accumulation of fat droplets in the control group. We could detect the selective accumulation of ^{10}B atoms in VX-2 tumour until 7 days after injection by neutron capture autoradiography. Tumour growth suppression was recognized with thermal neutron irradiation after intra-arterial injection of ^{10}B -containing WOW emulsion on VX-2 rabbit hepatic tumour models.

Results 2: Clinical Case: We had started the pilot clinical studies of BNCT to recurred hepatic cancer. In accordance with the clinical results of Higashi and colleagues, WOW emulsion has been used as the carrier of anti-cancer agents on intra-arterial injections in clinical trials. We would like to apply BNCT for the treatment of HCC in order to increase the selection of therapies available for HCC patients. We developed a ^{10}B -containing WOW emulsion using a double emulsification technique. We had performed first pilot clinical study for treating BNCT with ^{10}B -containing WOW emulsion to the patient with multiple HCCs. The patient had been performed right hepatectomy, and also hepatic arterial chemotherapies with epirubicin containing WOW emulsion were performed in the recurrence stages. The multiple tumours in the left liver lobe were treated with BNCT by selective intra-arterial infusion of ^{10}B -containing WOW emulsion. The pre-BNCT dosimetry was performed using SERA (mean tumour fluence is 12Gy-Eq on 56 minutes BNCT (Maximum 19Gy-Eq on tumour), and maximum fluence of normal mucosa is 5.0 Gy-Eq). The tumour size was remained stable during 3 months after BNCT, and tumour marker (AFP and PIVKA-II) was shown 20% decrease compared with pre-treated status. No adverse effect as a result of BNCT was observed during the treatment and follow-up period. The BNCT-treated tumours showed regrowth 3 months after BNCT, so the patient has continued the repeated hepatic arterial chemotherapy of epirubicin containing WOW emulsion.

Conclusions: The present results showed that ^{10}B -containing WOW emulsion can be applied as a novel intra-arterial boron carrier for BNCT to HCC.

O5-4

Efficacy and Safety of Nintedanib Versus Sorafenib in Caucasian and Asian Patients with Advanced Hepatocellular Carcinoma: Combined Analysis of Two Randomised Phase II Trials

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Background: Nintedanib is an oral, triple angiokine inhibitor of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) receptors. Nintedanib in combination with docetaxel is approved in the European Union for the treatment of patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after first-line chemotherapy. Two randomised, multicentre, open-label, Phase II studies evaluated the efficacy and safety of nintedanib versus sorafenib in Caucasian patients (NCT01004003; 1199.37) and Asian patients (NCT00987935; 1199.39) with advanced hepatocellular carcinoma (HCC).

Methods: Enrolled patients had unresectable, advanced HCC, ECOG-PS ≤ 2 , Child-Pugh score A, alanine/aspartate aminotransferase (ALT/AST) $\leq 2 \times$ upper limit of normal and

≥1 untreated measurable lesion or previously treated lesion with progression (by RECIST 1.0). Patients were randomised 2:1 to nintedanib 200 mg bid or sorafenib 400 mg bid continuously in 28-day cycles, until intolerable adverse events (AEs) or disease progression (PD); treatment beyond PD was allowed if clinical benefit was perceived. The primary endpoint was time to progression (TTP) by independent central review (ICR; RECIST 1.0); secondary endpoints included overall survival (OS) and objective tumour response (OR) by ICR. Safety was evaluated by the incidence and intensity of AEs (CTCAE 3.0).

Results: Across two trials, 188 patients received nintedanib (Caucasian: n = 62; Asian: n = 63) or sorafenib (Caucasian: n = 31; Asian: n = 32). Main patient demographics/baseline characteristics were balanced between treatments in both trials except for macrovascular invasion (nintedanib vs. sorafenib; 48% vs. 31%) and α -fetoprotein (AFP) levels (AFP >20 mg/l; 76% vs. 66%) in the Asian study. Thirty Caucasian patients and 21 Asian patients were treated beyond PD. TTP was comparable between nintedanib and sorafenib (median 3.7 vs. 3.9 months; HR 1.31 [95% CI: 0.89–1.91]), as were OS (median 11.4 vs. 11.0 months; HR 0.91 [95% CI: 0.65–1.29]) and OR rate (4% vs. 5%). The rate of patients with Grade ≥3 AEs (62% vs. 87%) and AEs leading to dose reduction (19% vs. 51%) was lower with nintedanib than with sorafenib; more nintedanib-treated patients had AEs leading to drug discontinuation (34% vs. 29%). The most frequent (>5% of patients in any group; nintedanib vs. sorafenib) Grade ≥3 AEs were diarrhoea (10% vs. 5%), fatigue (7% vs. 2%), increased AST (8% vs. 13%) and ALT (6% vs. 8%), anaemia (7% vs. 6%), malignant neoplasm progression (6% vs. 8%), thrombocytopenia (5% vs. 8%), skin reaction (1% vs. 6%) and palmar-plantar erythrodysesthesia syndrome (0 vs. 19%).

Conclusions: Combined analysis of two trials in Caucasian and Asian patients showed similar efficacy between nintedanib and sorafenib. AEs were as expected based on the safety profile of both agents; nintedanib-treated patients reported fewer Grade ≥3 AEs and AEs leading to dose reduction. Further studies of nintedanib in patients with advanced HCC are warranted.

O5-5

Ramucirumab as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma: East Asian Subgroup Analysis of the Phase III REACH Trial

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Background: The REACH trial did not demonstrate a significant improvement of overall survival (OS) for ramucirumab (RAM) versus placebo (PBO) in the second-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC) in the intent-to-treat (ITT) population (N = 565). However in a pre-specified group of pts with elevated (≥400 ng/ml) baseline α -fetoprotein (AFP), an improvement in OS was observed in the RAM arm (HR: 0.674). Results from an East Asia (EA) subgroup analysis are presented.

Methods: At randomization, pts were stratified by geographic region (Region 1, North America vs. Region 2, Europe vs. Region 3, EA) and etiology of liver disease (hepatitis B vs. hepatitis C vs. other etiologies). Region 3 consisted of the EA countries: Hong Kong (n = 24), Japan (n = 93), Philippines (n = 1), South Korea (n = 70), Taiwan (n = 58), and Thailand (n = 6). Both OS and progression-free survival (PFS) for EA pts were evaluated by the Kaplan-Meier method and hazard ratios (HRs) were calculated using a Cox regression model. The log-rank test was used to compare treatment arms. Objective response rates (ORRs) were compared using the Cochran-Mantel-Haenszel test. ClinicalTrials.gov number NCT01140347.

Results: Baseline pt characteristics and most prognostic factors of the 252 EA pts were similar to those of the overall ITT population and the baseline pt characteristics and most prognostic factors were similar between treatment arms in the EA pt subgroup. Median OS for EA patients was 8.2 months for the RAM arm and 6.9 months for the PBO arm (HR: 0.835, 95% CI: 0.634–1.100, p = 0.2046). Median PFS for EA patients was 2.2 months for the RAM arm and 1.5 months for the PBO

arm (HR: 0.721, 95% CI: 0.555–0.937, $p = 0.0141$). The ORRs were 6% (95% CI: 2.7–11.0) in the RAM arm and 0.8% (95% CI: 0.1–4.4) in the PBO arm ($p = 0.0298$). In EA pts with AFP ≥ 400 ng/ml ($n = 139$), the median OS was 7.8 months for the RAM arm ($n = 66$) and 4.2 months for the PBO arm ($n = 73$) (HR: 0.749, 95% CI: 0.519–1.082, $p = 0.1213$). Of the EA pts who received at least one dose of treatment ($n = 246$), the only grade ≥ 3 treatment-emergent adverse event occurring in $\geq 5\%$ of pts with a higher incidence for RAM ($n = 123$) than PBO ($n = 123$) was hypertension (8 [7%] vs. 1 [0.8%]).

Conclusions: This EA subgroup analysis indicates that treatment with RAM led to an improvement in PFS, and ORR, and demonstrated an acceptable safety profile in EA pts with advanced HCC. A greater OS benefit was observed in pts with baseline AFP ≥ 400 ng/ml, consistent with the results observed in the ITT analysis. Further evaluation of RAM in EA pts is warranted.

O6-1

Outcomes of Pure Laparoscopic Versus Open Hepatic Resection for Hepatocellular Carcinoma in Cirrhotic Patients: A Case-Controlled Study with Propensity Score Matching

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Background: Laparoscopic hepatic resection (LH) for hepatocellular carcinoma (HCC) has gradually gained ground as a safe and minimally invasive treatment, although LH for cirrhotic patients remains challenging. The aim of this study was to compare the short- and long-term outcomes of LH and open hepatic resection (OH) for HCC in case-controlled patient groups using the propensity score.

Methods: Between January 2007 and August 2014, 28 and 57 patients with histologically proven cirrhosis (histological activity index, fibrosis score 4) underwent pure LH and OH (less than segmentectomy) for peripheral HCC ≤ 5 cm, respectively. Because this study was retrospective, there was bias in treatment selection. To correct the difference in clinicopathological factors, including difficulty scores, between the two groups, propensity score matching (PSM) was used at a 1:1 ratio, which resulted in a comparison of 20 patients/group. We compared the short- and mid-term outcomes between these subsets to investigate the efficacy of LH.

Results: Clinicopathological variables, including difficulty score, were well-balanced between the two groups. The incidence of complications and mean intraoperative blood loss were lower in the LH group than the OH group (0% vs.

45% and 180 vs. 440 cc, $p = 0.001$ and 0.04 , respectively). The 3-year disease-free survival rate was 42% in the LH group and 30% in the OH group, respectively ($p = 0.533$), whereas the 5-year overall survival rates were 46% and 60%, respectively ($p = 0.606$).

Conclusions: LH is a safe and effective treatment option for cirrhotic patients with HCC in terms of intraoperative blood loss and morbidity.

O6-2

Local Control of Laparoscopic Hepatic Resection for Surface Hepatocellular Carcinoma: Comparison with Percutaneous Radiofrequency Ablation

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Background: Percutaneous radiofrequency ablation (P-RFA) therapy is a widely applied treatment for small hepatocellular carcinoma (HCC); however, local recurrence is a major issue of HCC located at the surface of the liver (surface HCC). The aim of this study was to compare the outcome of laparoscopic hepatic resection (LH) and P-RFA for surface HCC in case-controlled patient groups using the propensity score.

Methods: Between January 2011 and December 2013, 106 patients underwent LH for HCC at the Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine (Osaka, Japan), and 239 patients underwent P-RFA for HCC at the Department of Hepatology, Osaka City University Graduate School of Medicine (Osaka, Japan). In this study, we selected patients undergoing LH (less than segmentectomy) or P-RFA for surface HCC (≤ 3 cm in diameter, 1–3 nodules). Indication of inducing artificial pleural effusion and/or ascites for P-RFA were performed if necessary. A total of 40 patients who underwent LH (LH group) and 52 patients who underwent P-RFA (P-RFA group) met the inclusion criteria and were enrolled in the study. To correct the difference in clinicopathological factors between the two groups, propensity score matching was used at a 1:1 ratio, which resulted in a comparison of 27 patients/group. We compared outcomes between the two groups, with special reference to local recurrence.

Results: Clinicopathological variables were well-balanced between the two groups. One patient in the LH group was converted to open surgery due to adhesion. In the P-RFA

group, induced artificial pleural effusion and/or ascites was performed in 20 patients. There was no significant differences in the prevalence of post-treatments complications between the two groups (LH group, four (15%) cases vs. P-RFA group, 0 cases (0%); $P = 0.11$). All the postoperative complications in the LH group could be managed conservatively. The mean duration of hospitalization after treatment was significantly shorter in the P-RFA group than in the LH group (7.6 vs. 12.6 days, $P < 0.01$). No patients in the LH group experienced local recurrence; however, eight patients (30%) in the P-RFA group developed local recurrence 69 to 787 days after the P-RFA procedure (median; 245 days, $P = 0.004$). There was no significant difference in the incidence of local recurrence according to inducing artificial pleural effusion and/or ascites (with induced artificial pleural effusion and/or ascites, 35% (7/20) vs. without induced artificial pleural effusion and/or ascites, 14% (1/7), $P = 0.633$). The cumulative local recurrence rate at 1, 2, and 3 years was 0%, 0%, and 0% in the LH group, and 18.5%, 29.8%, and 38.6% in the P-RFA group, respectively ($P = 0.003$).

Conclusions: LH as well as P-RFA are safe treatments and LH was superior to P-RFA with regard to the control of local recurrence for surface HCC. Therefore, LH appeared to be an effective treatment for surface HCC.

O6-3

Laparoscopic Liver Resection for Hepatocellular Carcinoma with Liver Cirrhosis

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Background: Although the utility of laparoscopic liver resection for hepatocellular carcinoma (HCC) has been recognized in recent years, it is still unknown whether laparoscopic liver resection for HCC is suitable in cirrhotic patients. We introduced the technique and surgical outcomes of our apprehensive laparoscopic liver resection for HCC with liver cirrhosis.

Surgical Procedures: More careful attention was paid for the position of trocar insertion to preserve subcutaneous collateral circulation in cirrhotic patients. Liver mobilization area was minimized to preserve collateral blood and lymphatic flow. Hepatic parenchymal dissection was performed by VIO-CUSA with tissue select mode or Camp-Crashing using LCS under inflow occlusion (Pringle maneuver).

Results: We studied 93 patients separated into two groups according with or without liver cirrhosis histologically in the non-cancerous area of the resected specimen; with cirrhotic group (F4), 47 patients or non-cirrhotic group (F0-3), 46 patients retrospectively. Perioperative outcome

were analyzed in the two groups. There were no significant differences in the characteristics of patient's age, gender, type of infected hepatitis and histologically proven fibrosis in without cirrhosis group were F0; 3/F1; 14/F2; 14/F3; 15 patients respectively. Although the results of the preoperative liver function tests were significantly worsen in the cirrhotic group, no significant differences were observed between the two groups in the tumor size, operation time, and intraoperative blood loss. However the proportions of patients who were classified into Clavien's grade I was significantly higher in the cirrhotic group ($p < 0.005$), no significant differences were observed in the incidence of the postoperative complications, the proportions of patients who were classified into Clavien's grade II or above, and the duration of the postoperative hospital stay.

Conclusions: Even in the cirrhotic patients, laparoscopic liver resection with thoughtful procedure provides safe and better short-term outcomes for treating HCC.

O6-4

Surgical Outcome of Laparoscopic Liver Resection for Hepatocellular Carcinoma

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Background: Laparoscopic surgery offers a less invasive treatment procedure than open surgery does. We have applied laparoscopic surgery to liver resections for hepatocellular carcinoma, metastatic liver tumor, benign liver tumor and donor hepatectomy. Now, we report surgical outcomes of laparoscopic liver resections for hepatocellular carcinoma comparing with that of open surgery.

Patients and Methods: Using a prospectively collected database from 1997 to 2013, we analyzed the data of 72 consecutive cases of laparoscopic hepatectomy for hepatocellular carcinoma (PURE, $n = 38$; HYBRID, $n = 34$). The patients were 49 male and 23 female. We employed 27 cases treated by open hepatectomy during the same period as controls. The postoperative outcomes of patients with small (≤ 3 cm) hepatocellular carcinoma who received laparoscopic hepatectomy for the tumor were compared with those of matched 27 patients who received open hepatectomy for the tumor.

Results: There were no statistically significant differences in the age, sex, liver function, tumor size, or tumor location among the HYBRID, PURE, and OPEN groups. PURE was associated with lesser blood loss, lower weight of the resected liver, and a shorter skin incision than HYBRID and open hepatectomy [median blood loss (ml): PURE 10 ml,

HYBRID 380 ml and OPEN 450 ml], [weight of resected liver (g): PURE 24 g, HYBRID 63 g and Open 78 g]. The length of hospitalization in the cases treated by PURE and HYBRID hepatectomy was shorter than that in the cases treated by open hepatectomy [length of hospitalization (days): PURE 11 days, HYBRID 12 days, Open 17 days]. Postoperative morbidities (ascites and surgical site infection) were seen in one patient in HYBRID group. When comparing only in cases with primary solitary hepatocellular carcinoma, there were no significant differences in postoperative recurrence-free survival between the two groups.

Conclusions: These results showed that laparoscopic hepatectomy for hepatocellular carcinoma is not inferior to open hepatectomy in postoperative outcomes. These results suggested that the application of laparoscopic surgery to the liver resections is feasible.

O6-5

Safe Surgical Technique of Laparoscopic Hepatectomy Using Bipolar Hemostatic Sealer

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We reported a safe surgical technique and outcomes of laparoscopic hepatectomy (lap-HT) in our hospital. Total number of lap-HTs were 90 cases in our hospital. After mobilization of the right lobe with the patient in the half-lateral position, we resected the liver tissue using ultrasonic aspirator (UA) and bipolar hemostatic sealer (Aquamantys™ Bipolar®) for liver tumor in right lobe. This surgical instrument is useful for laparoscopic resection of the liver because of the vessel sealing technology. This bipolar sealer is a relatively new device that delivers RF energy coupled with saline solution irrigation for hemostatic sealing at lower temperatures (<100°C) than conventional electrocautery devices. This device functions to shrink the collagen in the walls of the tissue vessels without causing charring or burning, as opposed to standard electrocautery. In 90 cases of lap-HT, mean duration of surgery and mean blood loss were 332.9 minutes and 381 ml respectively. Mean duration of hospitalization after surgery were 12.1 days, and postoperative complications were five cases (5.6%). There were no intraoperative accidents and postoperative complications were minor. There was no postoperative mortality in all 90 cases. Comparing of clinical factor and short-term performance of surgery between open and lap-HT in patient with liver cirrhosis (ICGR15 $\geq$ 35%, 2002–2011), blood loss were significantly lower and hospital stay were significantly shorter in lap-HT patients. Laparoscopic resection of the liver can be safely performed using bipolar hemostatic sealer.

O6-6

Intraoperative Navigation by ICG Fluorescence Imaging in Patients with Laparoscopic Hepatic Resection

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Aims: Indocyanine green (ICG) has fluorescence when excitation light (wave length; 760 nm) and has been approved as fluorescent imaging agents in clinical setting. We used the ICG fluorescent image in laparoscopic hepatic resection and presented several topics involved in ICG image.

Methods: Between January 2002 and December 2014, we performed 110 cases of laparoscopic hepatic resection. We have introduced fluorescent laparoscopic system (KARL STORZ: IMAGE 1 SPIES™ Camera System) in February 2014. We injected ICG before operation or intraoperatively and used the system in either normal mode or fluorescent mode appropriately.

Results: 1. Detection of tumors: we identified and removed tumors safely by ICG fluorescent image, while such tumors were difficult to detect by normal image. 2. Detection of the boundary lines at the subsegment in the liver: we injected ICG intravenously after we clamped glisson sheath of the segment that we planned to resect and confirmed the line to resect. 3. Intraoperative cholangiography: by injection with diluted ICG preoperatively, we confirmed the form of bile duct that was pressed by huge liver cyst, leading to the navigation of resection line. 4. Test of bile leakage after resection: we examined the bile leakage by injecting diluted ICG into cystic duct postoperatively, deciding whether we need the drain apparatus or not.

Conclusions: It may be possible to improve the navigation with ICG image in laparoscopic hepatic resection to modify methods in its injection periods, dosages and others.

P1-01

**The Post-SIR-Spheres Surgery Study (P4S):
Liver Surgery Safely Performed in HCC
Patients Previously Treated with Selective
Internal Radiation Therapy (SIRT) Using Y-90
Resin Microspheres**

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Background: SIRT or radioembolization is increasingly
used for the treatment of Hepatocellular Carcinoma (HCC). It
was postulated that by inducing perihepatic or peritumoral
fibrosis, causing or worsening portal hypertension and/or by
inducing subclinical lung damage, SIRT renders liver surgery
more hazardous. This study aimed to evaluate liver surgery
safety after SIRT.

Methods: P4S is an international, multicentre retro-
spective analysis of outcomes associated with liver resection
(LR) or transplantation (LT) post-SIRT using Y-90 resin
microspheres (SIR-Spheres, Sirtex-Medical). Primary
endpoints were peri-operative and 90-day post-operative
morbidity and mortality. Data were captured on SIRT, surgery
and follow-up.

Results: The outcomes of 49 patients with HCC treated
by LR (n = 23) or LT (n = 26) were analyzed. Patients were
mainly cirrhotics (LR 61%; LT 92%). Nearly ¼ (24%) was
previously submitted to other procedures: TACE (18%),
resection (4%) or ablation (2%), chemotherapy pre-/post-

SIRT (9%) and portal vein thrombosis or occlusion (8%).
For SIRT, 18% received ≥2 sessions and 27% received SIRT
to whole liver. Pre-surgery, 20% had total bilirubin CTC
grade ≥2, 74% had comorbidities (mostly diabetes, hyper-
tension and cardiopathy). Median ASA score was 3 (ASA ≥3:
LR 61%; LT 81%). LR included minor (35%), major not
extended (48%) and extended resections (17%); 8% of LT
patients had living-related donor LT. Median time from last
SIRT to surgery was 8.0 (LR) and 7.4 (LT) months. Median
post-operative stay [IQR] was 8.0 [4.0] (LR) and 11.0 [8.0]
(LT) days. The incidence of complications grade ≥3 was 4%
(LR) and 15% (LT). Pulmonary-specific complications
occurred only in 1 patient (LT; grade 2) and was not poten-
tially related to prior SIRT. Any grade liver failure was only
observed in LT (3.8%; 1 grade 2). 90-day readmission rates
were 4% (LR) and 27% (LT) while no 90-day all-cause
mortality was observed in either group. Median survival
from the time of surgery was not reached in any group with
median post-surgery follow up of 28.5 (LR) and 23.7 (LT)
months.

Conclusions: SIRT using SIR-Spheres did not increase
morbidity/mortality after liver resection/transplantation.

P1-02

**Impact of BCAA Supplementation on
Functional Liver Regeneration for Patients
Undergoing Portal Vein Embolization
Followed by Major Hepatectomy:
A Randomized Control Trial**

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Background: Portal vein embolization (PVE) can
decrease the resection ratio for major hepatectomy. Branched
chain amino acids (BCAAs) can promote hepatocyte regener-
ation. We analyzed BCAAs' effects, in terms of liver function
and liver regeneration after PVE in combination with major
hepatectomy.

Methods: To estimate sample size, we assumed the effect
of BCAA supplementation on liver regeneration to give an
increase in SPECT value of around +30%. Additionally, the
rate of functional liver volume after PVE at 1 month was 55 ±
14%. To detect the effectiveness of BCAA with a power of 80%

and a two-sided alpha level of 0.05, we calculated that 13 patients would be required in each study arm. This randomized control trial was conducted for patients receiving PVE through to complete hepatectomy from September, 2011 to June, 2013. BCAA granules were added three times a day to a conventional diet in BCAA group. The primary endpoint was functional liver regeneration of the future remnant liver after PVE followed by major hepatic resection. Functional liver regeneration was assessed by liver uptake value (LUV) obtained from ^{99m}Tc -GSA scintigraphy single-photon emission computed tomography (SPECT)/CT fusion images. Secondary endpoints were volumetric liver regeneration and changes in liver function and laboratory data. The Institutional Review Board approved this prospective randomized control trial (number 1142).

Results: BCAA administration group (BCAA group; $n = 13$) and non-BCAA group (control group; $n = 15$) were investigated. The median number of days of BCAA administration was 116 (82–333). Background factors were almost identical. The primary endpoint was partially met: LUV significantly increased in BCAA group compared with control group 6 months after hepatic resection (266.7% vs. 77.6%, $P = 0.04$) and marginally increased after PVE (43.8% vs. 17.4%, $P = 0.079$). Following PVE, uptake ratio increments of the liver to liver plus heart at a 15-min (LHL15) decrease was significantly lesser in BCAA group compared with control group (0.0 and 0.01, $P = 0.023$).

Conclusions: We firstly demonstrated that BCAA supplementation significantly improved functional liver regeneration and liver function in patients undergoing PVE followed by major hepatic resection.

P1-03

Perioperative Single Dose Ertapenem Preventing Surgical Site Infection in Patients with Hepatocellular Carcinoma: A Retrospective Study

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Aim: Postoperative antibiotic prophylaxis is commonly believed to be effective in preventing postoperative surgical site infection (SSI), but very few studies have evaluated the usefulness of ertapenem prophylaxis after liver resection. A retrospective study was conducted to evaluate the role of ertapenem versus other standard antibiotic prophylaxis in patients with hepatocellular carcinoma undergoing hepatectomy.

Methods: This study was retrospectively analyzed the clinical data of 118 patients with hepatocellular carcinoma who underwent liver resection at our single center between

January 2012 and December 2013. The patients were divided into ertapenem group ($n = 54$) and nonertapenem group ($n = 64$). The ertapenem group was only given a single dose ertapenem preoperatively as perioperative prophylaxis. The nonertapenem group was given other antibiotics from the preoperative half an hour until the temperature back to normal for 3 days. Results and outcomes in the two groups were compared.

Results: Groups were similar with respect to age (54.3 vs. 54.9, $P > 0.05$), gender and type of liver resection. There were no significant differences between the two groups in the incidence of surgical site infection (7.4% vs. 9.3%, $P > 0.05$), systemic inflammatory response syndrome (12.1% vs. 10.7%, $P > 0.05$), C-reaction protein on 3 days after surgery (64.9 mg/l vs. 58.3 mg/l, $P > 0.05$) and the duration of hospital stays postoperatively (11.6 days vs. 12.4 days).

Conclusions: Postoperative antibiotic prophylaxis cannot prevent surgical site infection after hepatectomy. The patients with hepatocellular carcinoma given single dose of ertapenem for perioperative prophylaxis suffered low rates of SSI, and needn't unnecessary antibiotic prophylaxis postoperatively.

P1-04

A Role of Intra-Arterial Chemotherapy as a Part of Multidisciplinary Treatment for Advanced HCC

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Aim: The prognosis of advanced HCC is still poor, and prognostic factors are mainly liver function, tumor burden and treatments. We retrospectively studied a result of advanced HCC with preserved liver function, and analyzed treatment allocation.

Study Design: We treated 723 patients with HCC during 2000–2012. Among these, 55 patients were selected in this study following criteria: Child-Pugh A and B7, and tumor stage of UICC ver.7 IIIA (17 patients), and IIIB (38 patients). We treated them initially hepatic resection or hepatic-arterial infusion chemotherapy (HAIC) using CDDP and 5-FU from a chemo-port as induction chemotherapy for down-staging and/or sizing, and if effectively converted, we referred them for surgical resection, and if not, we treated them continuously using interventional techniques including radiotherapy.

Results: Four HCC patients were initially resected, and the rest of 51 patients were firstly treated by HAIC. Among these 51 patients, 9 patients (18%) were effectively converted for resection (2 (12%) out of 15 IIIA patients and 7 patients (20%) out of 36 IIIB patients), and were successfully resected. Three- and 5-year survival rates of these 9

patients were 100% and 60%, respectively, and it was significantly better than the survivals after hepatic resection mono-therapy.

Discussion and Conclusions: The prognosis of advanced HCC is still poor, however, a preoperative treatment using regional chemotherapy might select effectively a patients for hepatic resection with responseguide therapy. And it may also exclude a silent distant metastasis, and select a liver limited tumor burden effectively (Test of time). Repeated injection of various drugs consecutively from a chemo-port may allow a test of sensitivity for chemo-drug (Test of chemo-sensitivity). Finally, if advanced HCC was effectively converted, a more promising treatment such as resection, transplantation, TACE and ablation should be allocated for the prolongation of patient's survival.

P1-05

Impact of Preoperative One-Shot Hepatic Arterial Chemotherapy on Oncologic Outcome of Resection for Primary and Recurrent Hepatocellular Carcinoma with Extensive Vascular Invasion

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Introduction: Hepatocellular carcinoma (HCC) with extensive vascular invasion is rarely amenable to resection and even in resected patients the outcome is generally poor. We retrospectively studied the impact of preoperative hepatic arterial one-shot infusion of carboplatin, adriamycin and mitomycin (CAM) on the outcome of resection in this group of patients.

Patients and Methods: In a total of 62 patients, we resected primary and recurrent Vp3-4 and Vv2-3 HCCs. In these patients, tumors were resected by major hepatectomies in conjunction with extirpation of tumor thrombi inside the vessels. Of the resected 62 patients, 52 received CAM preoperatively and 10 did not (surgery-alone group). The anti-cancer effect of CAM was diagnosed with imaging and tumor markers on the 14th day after treatment. Of the 52, 25 were diagnosed to be CAM-effective (CAM-effective group), while in the other 27, CAM was not effective (CAM-ineffective group). Survival and recurrence were compared among the above three groups. Also in 4 patients with recurrence after other treatments with RFA, TACE and HAIC, we studied the impact of CAM on oncologic outcome after resection. Prognostic factors for post-resection outcome were investigated using univariate and multivariate analyses.

Results: CAM was well tolerated with minimal side effects in all patients. Overall survival in primary resection cases was 32%, 16%, 8%, and disease-free survival was 18%,

7%, 4%, at 1, 3, 5 years in the 62 patients. Overall 5-year survival in surgery-alone, CAM-ineffective and CAM-effective groups was 0%, 0% and 23% ($p < 0.0001$), and 50% survival time was 3, 6 and 30 months, respectively. Disease-free 3-year survival was 0%, 0% and 16% ($p = 0.004$), and 50% disease-free survival time was 2, 1.5 and 10 months, respectively. These results suggest significantly better post-resection oncologic outcome in CAM-effective group. Mode of recurrence was different between CAM-effective and CAM-ineffective groups. No recurrence was observed in 5 patients only in the former group. The rate of extrahepatic recurrence was significantly lower in the former group (30% vs. 53%, $p = 0.001$). The response to CAM was identified to be a significant and independent prognostic factor for post-resection survival. Out of 4 patients with previous treatments other than resection, 2 were CAM effective and lived longer than 1 year after resection.

Conclusion: Tumor response to CAM may predict oncologic outcome of resection for HCCs with extensive vascular invasion. CAM may be a simple and safe method to select surgical patients and to potentially improve their cancer outcome.

P1-06

The Comparison of Oncologic and Clinical Outcomes of Laparoscopic and Open Liver Resection for Hepatocellular Carcinoma

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Purpose: We evaluate the operative outcome and oncologic outcome of laparoscopic liver resection for hepatocellular carcinoma (HCC), and compare with open liver resection.

Method: From January 2004 to February 2013, clinical data of 121 patients who underwent laparoscopic liver resection for HCC (Laparoscopic liver resection group, lapa-group) were collected from two medical centers in Daegu and analyzed retrospectively. Control group (Open liver resection group, open-group) were retrospectively matched, and compared with lapa-group.

Results: Laparoscopic major liver resections were performed in 6 patients. Laparoscopic anatomical resections and non-anatomical resections were performed in 72 patients, and 49 patients, respectively. Mean operative time was shorter in lapa-group, mean intraoperative transfusion rate and total amount were small in lapa-group. In lapa-group and open-group 3-year disease free survival rate (DFS) were $58.3 \pm 0.08\%$, and $62.6 \pm 0.06\%$, respectively. (p -value = 0.773) In lapa-group and open-group 3-year overall survival rate (OS) were $65.3 \pm 0.8\%$, and $65.7 \pm 0.6\%$, respectively. (p -value = 0.610).

Conclusion: Laparoscopic liver resection for HCC is feasible and safe in a large number of patients, with reasonable operative and oncologic results.

different East Asian countries. These differences impact both the eligibility to receive potentially curative therapy and the prognosis of patients with HCC.

P1-07

Comparison of the Outcomes of Hepatocellular Carcinoma After Hepatectomy Between Two Regional Medical Centers in China and Japan

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Background: Hepatocellular carcinoma (HCC) is a common malignant disease of the liver in China and Japan. The purpose of this study was to compare the outcomes of HCC patients after hepatectomy between two regional medical centers in China and Japan.

Methods: The clinical data of HCC patients who underwent hepatectomy were collected from the Department of Hepato-Biliary & Pancreatic Surgery, The 2nd Hospital Affiliated of Nanchang University, China and the Department of Surgery, Nagasaki University Hospital, Japan. The patient and tumor characteristics, etiology, and overall survival rates after hepatectomy were investigated. A Kaplan–Meier analysis assessed the survival between the groups.

Results: There were 270 patients who had been diagnosed with HCC and underwent subsequent hepatectomy in the Nanchang group (from 2005~2014), and 380 patients in the Nagasaki group (from 1992~2014). The two different regional groups had varied liver disease background. There were 88% (237/270) and 25% (94/380) hepatitis B virus infection patients, 0.3% (1/270) and 37% (141/380) hepatitis C virus infection patients, and 11% and 27% NonBNonC-HCC patients in the Nanchang group and the Nagasaki group, respectively. The presence of large tumors (>5 cm), tumor capsule and a high AFP value (≥ 400 U/L) were more frequent in the Nanchang group compared with in the Nagasaki group ($P < 0.05$). In the outcome analysis, the Nanchang group showed an overall poorer survival than the Nagasaki group (the 1-, 3-, 5-years overall survival rates were 80.3%, 62.9% and 55.6% in the Nanchang group and 88.8%, 75.4%, and 61.1% in the Nagasaki group respectively, $P < 0.05$).

Conclusion: Significant differences in the clinicopathologic features and outcomes existed among HCC patients from

P1-08

Long-Term Outcomes of Hepatocellular Carcinoma After Curative Resection in Patients with Cirrhotic Versus Non-Cirrhotic Backgrounds

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Background/Aims: There are little long-term data on the prognosis of hepatocellular carcinoma (HCC) after curative resection for cirrhotic versus non-cirrhotic backgrounds. We aimed to compare clinical outcome between those with cirrhosis and without at the time of surgery.

Methods: Regardless of the cause of HCC, 610 patients who underwent surgical resection for HCC from January 1996 to December 2012 were classified into cirrhosis ($n = 318$, 52.1%) and non-cirrhosis ($n = 292$, 47.9%) groups. Their long-term postoperative outcomes and prognostic factors were compared.

Results: The median age was 53.3 years (480 men). The most common cause of HCC was chronic hepatitis B virus (HBV) infection ($n = 380$, 62.3%). Comparing the two groups, the postoperative overall survival (OS) and disease-free survival (DFS) rate were superior in the non-cirrhotic group. During the follow-up (median 136 months), 10-year postoperative OS and DFS were 56.9% and 39.3% in the cirrhosis group versus 63.0% and 48.6% in the non-cirrhosis group (all $P < 0.05$). The underlying etiologies did not influence the clinical outcomes. Furthermore, among those with HBV-related HCC, antiviral therapy influenced neither OS nor DFS.

Conclusions: The clinical outcome after hepatic resection for HCC was affected by background liver status in patients with HCC. The preventive effect of antiviral therapy on the HCC recurrence need to be further studied.

P1-09

The Survival Outcomes of Hepatic Resection Compared with Transcatheter Arterial Chemoembolization or Sorafenib for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Background: The treatment of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) remains controversial. We compared the outcomes of sorafenib therapy, hepatic resection, and transarterial catheter embolization (TACE) for the treatment of HCC with PVTT.

Methods: Patients who were diagnosed with HCC with PVTT between January 2000 and December 2011 and received sorafenib, hepatic resection, or TACE were included. Patients with main portal vein tumor thrombosis, superior mesenteric vein tumor thrombosis, or Child-Turcotte-Pugh (CTP) score C were excluded. Records of 172 patients were analyzed, retrospectively. Forty, 80, and 52 patients received hepatic resection, TACE, hepatic resection, and TACE respectively. PVTT was classified as either involving the segmental branch (type I) or extending to involve the right/left portal vein (type II).

Results: The median survival times in the hepatic resection, TACE and sorafenib groups were 19.9, 6.6 and 6.2 months, respectively ($p < 0.001$). One-, 2-, and 3-year overall survival rates were 63.6%, 31.3%, and 30.0% in the hepatic resection group; 36.3%, 9.8%, and 8.6% in the TACE group; and 32.3%, 5.6%, and 0.0% in the sorafenib group ($p < 0.001$). The tumor size, PVTT site type, presence of ascites, and alpha-fetoprotein level were associated with the prognosis of HCC with PVTT.

Conclusion: As compared with TACE and sorafenib, hepatic resection may prolong the survival of patients with HCC with PVTT involving the segmental branch.

P1-10

Prognostic Value of the Modified Glasgow Prognostic Score in Patients Undergoing Radical Surgery for Hepatocellular Carcinoma

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Background: There is increasing and consistent evidence concerning the association of systemic inflammation and poor outcome in patients with hepatocellular carcinoma (HCC). The aims of this study were to identify a superior inflammation-based prognostic scores for patients with HCC undergoing hepatectomy.

Methods: We analyzed two independent cohorts including a total of 723 patients with HCC who underwent radical surgery between 2010 and 2012. The prognostic value of the inflammation scores including the Glasgow Prognostic Score (GPS), modified GPS (mGPS), neutrophil to lymphocyte ratio, platelet lymphocyte ratio, Prognostic Index, and Prognostic Nutritional Index and staging systems including Barcelona Clinic Liver Cancer and Cancer of the Liver Italian Program scores was analyzed in a test cohort of 367 patients and validated in a validation cohort of 356 patients.

Results: The high score of mGPS was associated with large tumor size, vascular invasion and advanced clinical stages. Multivariate analysis showed that the mGPS had an independent association with overall survival and disease free survival and had a higher AUC value in comparison with other inflammation – based scores.

Conclusion: This study demonstrates that the mGPS is an independent marker of poor prognosis in patients with resectable HCC and is superior to the other inflammation-based scores.

P1-11

Safety and Efficacy of ALPPS for Hepatocellular Carcinoma

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Background: The introduction of Associating Liver Partition for Portal Vein Ligation and Staged Hepatectomy (ALPPS) has revolutionized the surgical management of small-for-size future liver remnant (FLR) contemplating for major hepatectomy in patients with colorectal liver metastasis. However, there is limited data on its application in hepatocel-

lular carcinoma (HCC). Our aim was to determine the outcome of ALPPS in patients with hepatitis B-related HCC.

Methods: The selection criteria were Child-Pugh A liver cirrhosis, indocyanine green (ICG) retention rate <20% at 15 minutes, FLR/ESLV <40%, and platelet count $\geq 100 \times 10^9/L$. Our ALPPS approach entailed right portal vein ligation and in-situ split along the Cantle's line for extended right hepatectomy, or right side of falciform ligament for right trisectionectomy by the anterior approach, with complete split down to inferior vena cava using ultrasonic dissector. No Pringle maneuver, plastic bag, drain nor silicone sheets were used after stage I. In stage II, the right liver was mobilized after division of the right hepatic artery, hepatic duct and hepatic veins.

Results: From October 2013 to February 2015, a total of 17 patients [median age 62 (50–80)] with hepatitis B-related hepatocellular carcinoma underwent the ALPPS procedure with the anterior approach (Table 1). The baseline FLR volume was 297 ml (i.e. FLR/ESLV = 24.2%) and ICG retention rate was 12.8%. The median tumor size was 6.0 cm. After a median of 6 days, the left FLR hypertrophied by 48.7% in volume to 509 ml (i.e. FLR/ESLV = 38.5%). All patients proceeded to second stage hepatectomy (extended right hepatectomy, n = 8; right hepatectomy, n = 6; right trisectionectomy, n = 3) without significant adhesion encountered. There was no evidence of bile leakage. Median blood loss for stage I and II were 500 (100–2000) ml and 600 (30–8000) ml respectively. Median operating times for stage I and II were 360 (160–577) minutes, and 150 (64–344) minutes respectively. The overall morbidity (Clavien-Dindo grade III or above) was 11.8% (n = 2, intestinal obstruction and pneumothorax), and hospital mortality rate was 5.9% (n = 1, multiorgan failure).

Conclusion: The ALPPS procedure was efficacious for patients with chronic liver diseases. It can be safely performed by the anterior approach.

several diagnostic tools for the detection of biliary complications. Magnetic resonance cholangiopancreatography (MRCP) is known to be an accurate method in the evaluation of the biliary system. In addition, most biliary complications are addressed by biliary intervention. However, the value of MRCP findings to predict biliary intervention after liver transplantation has not been studied. In this study, we assessed the value of MRCP imaging taken one month after LDLT for the prediction of possible biliary intervention. We selected 201 patients who underwent LDLT from 2006 to 2010 in single medical center. An MRCP was taken 1 month after LDLT. MRCP images were analyzed for angle of anastomosis in 3D image, presence of filling defect, length of filling defect in maximum intensity projection (MIP) image, presence of intra-hepatic bile duct dilatation, biliary stricture and leakage. Angle of anastomosis was defined as angle between donor site bile duct and recipient's common bile duct. Thereafter, we determined which patients underwent biliary interventions like ERCP or PTBD. Patients were followed up until December 31, 2012. Of which, 94 developed biliary complication. In multivariate analysis using Cox-regression method, anastomosis method (hazard ratio, 2.125; 95% CI, 1.371 to 3.292; P = 0.041), filling defect in MIP image (hazard ratio, 2.125; 95% CI, 1.371 to 3.292; P = 0.001), leakage (hazard ratio, 2.993; 95% CI, 1.215 to 7.374; P = 0.017), CBD stone (hazard ratio, 7.039; 95% CI, 1.651 to 30.012) and decreased angle of anastomosis site (hazard ratio, 0.987; 95% CI, 0.981 to 0.993; P < 0.001) at MRCP taken 1 month after LDLT were significant predicting factors for biliary intervention. Cut-off value for angle of anastomosis was 106.45° with 62.8% sensitivity and 77.6% specificity. From MRCP images taken 1 months after LDLT, decreased angle of anastomosis as well as filling defect in MIP image and biliary leakage, is associated with increased risk of biliary intervention.

P1-12

MRCP at One Month After LDLT May Predict Biliary Intervention

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Biliary complications are common and is an important complication after living donor liver transplantation (LDLT). One such example is biliary leakage after LDLT. There are

P1-13

Interleukin-2 Receptor Antagonist Immunosuppression and Consecutive Viral Management in Living Donor Liver Transplantation for Hepatitis C/Human Immunodeficiency Virus Co-Infected Patient

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Background: The time from HCV infection to the development of HCC is shorter in the setting of HIV co-infection. HIV infection accelerates the progression of liver fibrosis and

attenuates the efficacy of interferon treatment for HCV. Although liver transplantation is a therapeutic option for end-stage liver disease with HCC, living donor liver transplantation (LDLT) for HCV/HIV co-infected patients is still challenging. One concern is that postoperative HCV/HIV management on immunosuppression was not established in liver transplantation. The aim of the present study was to investigate the feasibility of consecutive administration of early calcineurin inhibitor-free immunosuppression including interleukin-2 receptor antagonist (IL2Ra), interferon/ribavirin preemptive and antiretroviral therapy (ART) in LDLT.

Methods: LDLT was performed for 2 HCV/HIV co-infected end-stage liver disease patients. Immunosuppression consisted early calcineurin inhibitor-free with IL2Ra and methylprednisolone. Maintenance low dose of tacrolimus was started a week after LDLT. ART was also re-started around a week after LDLT with tacrolimus blood trough level monitoring. A month after LDLT, pegylated interferon and ribavirin therapy were added.

Results: 47-year-old male (first case): HCV/HIV co-infection was found at the age of 22. Model for end-stage liver disease score was 22 at the time of LDLT. Total bilirubin and HCV-RNA level were 3.8 mg/dl and 6.5 LogIU/ml. He achieved undetectable HIV-RNA on ART (raltegravir, lamivudine, abacavir and etravirine). In 2013, LDLT was performed and IL2Ra and methylprednisolone were administered. The graft weight was calculated to be 39% of patient standard liver volume. Tacrolimus was started on day 8. Pegylated interferon and ribavirin were added on day 28. Postoperative course was uneventful. He was discharged on day 43. HCV-RNA and HIV-RNA were undetectable at 17 months after LDLT. 50-year-old male (second case): HCV/HIV co-infection was found at the age of 41. Model for end-stage liver disease score was 13. Total bilirubin and HCV-RNA level were 3.4 mg/dl and 3.7 LogIU/ml. He achieved undetectable HIV-RNA on ART (raltegravir, tenofovir and emtricitabine). In 2014, LDLT was performed. Immunosuppression protocol was same as the first case. The graft weight was calculated to be 35% of patient standard liver volume. Tacrolimus was started on day 6. Postoperative course was uneventful. He was discharged on day 38. Pegylated interferon and ribavirin were added on day 46. HCV-RNA and HIV-RNA were undetectable at 8 months after LDLT.

Conclusions: The early calcineurin inhibitor-free with IL2Ra and methylprednisolone in LDLT may be suitable for HCV/HIV co-infected patient. Consecutive HCV/HIV management was successful.

P1-14

Prognostic Nutritional Index (PNI) Predicts the Surgical Outcomes of Hepatocellular Carcinoma, Especially in Hepatitis C Patients

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Background: The prognostic nutritional index (PNI), that is one of the inflammatory and immunonutritional indices: $10 \times \text{Albumin (g/dl)} + 0.005 \times \text{total lymphocyte } (\mu\text{L})$, has been shown to be a prognostic marker in several gastrointestinal malignancies. The aim of this study is to evaluate the relationship between the PNI and survival in patients with hepatocellular carcinoma (HCC), especially in hepatitis C virus (HCV) positive patients.

Patient and methods: The 209 consecutive cases, who received hepatectomy for primary HCC from January 2000 to December 2013, were divided into two groups according to PNI: High-PNI group (PNI ≥ 45 , $n = 105$) and Low-PNI group (PNI < 45 , $n = 104$). Among them, HCV positive patients (96 cases) were also divided into the two groups according to PNI: High-PNI ($n = 40$) and Low-PNI ($n = 56$). Patient background and surgical outcomes were compared between the two groups.

Results: In the whole patient analysis, age and male patient ratio were significantly higher in High-PNI group than in Low-PNI group. In hepatic function, ICGR15 was significantly lower in High-PNI group than in Low-PNI group. In the tumor status, tumor size was significantly larger and PIVKA-II level was significantly higher in Low-PNI group than in High-PNI group. Perioperative course was not different between the two groups. Patient survival was significantly lower in Low-PNI group than in High-PNI group: 58% vs. 71% in 5-year survival ($p = 0.047$). Progression free survival was also significantly lower in Low-PNI group than in High-PNI group: 22% vs. 41% in 5-year survival ($p = 0.0014$).

In the HCV positive patient analysis, patient background, liver and tumor status and perioperative course were not different between the two groups. Patient survival was significantly lower in Low-PNI group than in High-PNI group: 56% vs. 82% in 5-year survival ($p = 0.02$). Progression free survival was also significantly lower in Low-PNI group than in High-PNI group: 19% vs. 40% in 5-year survival ($p = 0.05$). In the HBV positive and non-B non-C patients, long-term survival did not differ between High- and Low-PNI groups.

Conclusions: In the whole patient analysis, PNI was related to impaired hepatic function and tumor progression. PNI can predict the surgical outcomes after hepatectomy for HCC, especially in HCV positive patient.

P1-15

Combination of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio Is a Useful Predictor of Postoperative Survival in Patients with Hepatocellular Carcinoma

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Background: The presence of systemic inflammation, elevation of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), has been reported to correlate with poor survival in various types of cancers, because the systemic inflammatory response may cause an aberrant release of proinflammatory cytokines, predisposing proliferation and metastasis of the tumor. Furthermore, combination of platelet count and neutrophil to lymphocyte ratio was reported to be a useful predictor of postoperative survival in patients with colorectal cancer (Ishizuka BJC 2013). However, hepatocellular carcinoma (HCC) was generally accompanied by cirrhosis and portal hypertension leading to hypersplenism and thrombocytopenia, and the relationship between PLR and prognosis in patients with HCC still remains unclear. We investigated the usefulness of a novel inflammation-based prognostic system: CNP (the combination of NLR and PLR) for predicting survival in patients with primary HCC.

Materials and Methods: The medical records of 209 patients who had been underwent hepatectomy for primary HCC at the Mie University Hospital, between January 2000 and December 2013 were reviewed. The CNP was calculated on the basis of data obtained before surgery; the HCC patients with both elevated NLR (>2.0) and PLR (>120) were allocated a score of 2, and patients showing one or neither were allocated a score of 1 or 0, respectively.

Results: The patients were classified to CNP 0 ($n = 76$), CNP 1 ($n = 55$), and CNP 2 ($n = 78$), respectively. Among three groups, there was no significant differences in age, gender, Child-Pugh score, tumor markers, tumor size, the number of the tumors, pathological findings, except for the indocyanine green retention rate at 15 min (CNP 1 vs. CNP 2: 16.9% vs. 12.5%, $p = 0.012$). The proportion of the patients with tumors beyond Milan criteria was lower in CNP 0 (25.0%) and CNP 1 (29.1%) than in CNP 2 (59.0%) ($p < 0.001$). Although the operation time was shorter in CNP 0 (327 min.) than in CNP 2 (376 min.) ($p = 0.014$), no significant differences were found in blood loss and morbidity. The 3-year overall survival in the CNP 0, CNP 1, and CNP 2 groups were 86.1%, 84.8%, and 62.8%, respectively (CNP0 vs. CNP2: $p = 0.007$, CNP1 vs. CNP2: $p = 0.003$). The 3-year disease free survival in the CNP 0, CNP 1, and CNP 2 groups were 54.3%, 37.9%, and 36.4%, respectively (CNP0 vs. CNP2: $p = 0.026$). Multivariate analyses

showed that CNP and multiple tumors were a significant independent risk factors for overall survival as well as disease free survival.

Conclusion: The CNP is considered to be a useful predictor for overall and disease free survival in patients with primary HCC.

P1-16

Importance of Screening for Esophagogastric Varices in Naïve HCC Within Milan Criteria: Clinical Factors Indicating Liver Transplantation

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Background/Aim: The shortage of donors in liver transplantation (LT) for hepatocellular carcinoma (HCC) is an important limitation, thus surgical resection and radiofrequency ablation (RFA) are performed as curative treatment for HCC within the Milan criteria (MC) instead of LT. However, recurrence beyond MC or early death is often observed in such cases. Here, we evaluated the clinical factors indicating LT.

Methods: From January 2007 to December 2013, 422 naïve HCC within MC who underwent upper gastrointestinal endoscopy examinations, and were treated with resection or RFA were enrolled. Esophagogastric varices (EGV) was classified into 3 types; small straight (grade 1), enlarged tortuous (grade 2), and large coil-shaped (grade 3). EGV over grade 2 were classified as clinically significant. Clinical backgrounds and laboratory data in relation to prognosis were examined.

Results: Positive for EGV, albumin <3 g/dl, prothrombin time (PT) $<70\%$, multiple tumors, Child-Pugh B, AFP >100 ng/ml, AFP-L3 $>10\%$, and PIVKA-II >100 mAU/ml were shown to be independent risk factors for recurrence beyond MC or death in univariate Cox-hazard analysis, while positive for EGV (HR 1.54), multiple tumors (HR 1.74), AFP-L3 $>10\%$ (HR 1.70), and PIVKA-II >100 mAU/ml (HR 1.70) were also revealed in multivariate analysis. To elucidate the importance of EGV, the subjects were divided into the V-group ($n = 87$) and non-V-group ($n = 335$). Following curative therapy, the recurrence rates beyond MC and death related to liver condition were higher in V-group than non-V-group (Figure: $P < 0.01$ and $P = 0.025$, respectively).

Conclusion: Because existence of EGV was an important factor for predicting early recurrence of HCC beyond MC and early death, early LT should be considered in the cases with EGV.

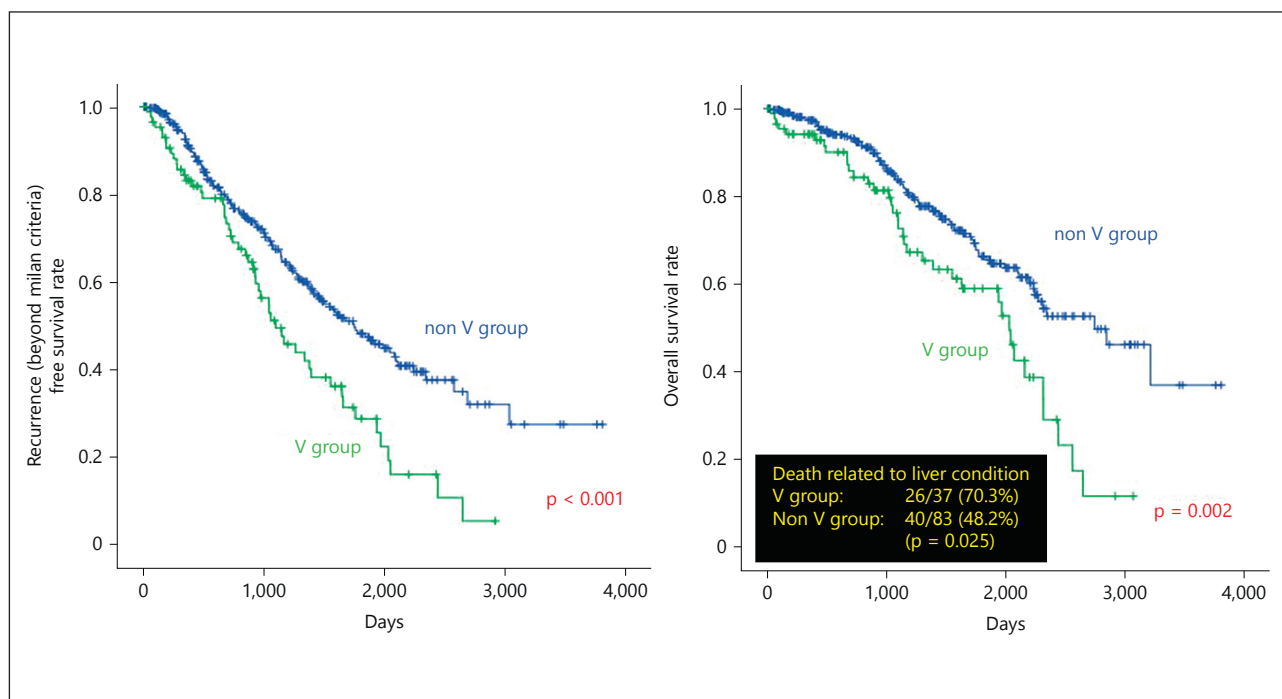


Fig. 1. (for Abstract P1-16).

P1-17

Experience of Laparoscopic Liver Resection Using with Fewer Energy Devices for Liver Tumor

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Background: Many kinds of energy device (ED) recently are developed, and adapted for laparoscopic liver resection. Not much, however, has been done to clarify how many kinds of ED should be used when the laparoscopic liver resection would be performed frugally, and safely.

Methods: During recent 5 years, we performed 33 laparoscopic minor hepatectomies (28 partial resections and 5 lateral segmentectomies). The 33 cases consisted of 20 men and 13 women, and the average age was 65-years-old. Child-Pugh score of the cases consisted of 20 A, and 13 B, and the average diameter of the tumor was 2.2 cm. Under 10 mm H₂O intraabdominal pressure, hepatic parenchyma was coagulated and Glisson's sheath was sealed using RFBC via three/four trocars stabbed. The coagulation/seal and dissection were operated alternately, and the liver resection was performed. As EDs, an ultrasonic dissection (US), a radiofre-

quency bipolar coagulation (RFBC), an ultrasonic surgical aspirator (CUSA), and a microwave coagulation (MW) were used in the 33 laparoscopic hepatectomies. On the viewpoint of the ED used, we analyzed number of ED used, operation time, blood loss, postoperative complication, and days in hospital.

Results: The mean operative time of the laparoscopic hepatectomy was 208 minutes, the mean blood loss was 140 cc, and the mean days in hospital were 10 days. No patient had postoperative complication. Number of ED used in laparoscopic hepatectomies were one in 3 cases, 2 in 27 cases, and 3 in 3 cases. Between the numbers of ED used, there was no significant difference in operation time, blood loss, postoperative complication, or days in hospital. Of the 27 cases which were performed using with 2 kinds of ED, the combination of US and RFBC were adapted in 21 cases. There was no significant difference in operation time, blood loss, postoperative complication, or days in hospital between the other kinds of combination such as MW/RFBC, and MW/CUSA.

Conclusion: The present results indicate that operators would not need to use many kinds of ED in a laparoscopic hepatectomy. Apply of two EDs, which is the combination of coagulative sealer and coagulative dissector (e.g., RFBC/US), would contribute to skillful and safe laparoscopic hepatectomy.

P1-18

Short-Term Results of Laparoscopic Multipolar Radiofrequency Ablation for Hepatocellular Carcinoma

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Background: Radiofrequency ablation (RFA) has played a key role in the management of small hepatocellular carcinoma (HCC) worldwide. Multipolar RFA (CelonPOWER System; Olympus Medical Systems, Japan) was approved in 2012 in Japan and we have performed laparoscopic RFA (LRA) using a multipolar RFA system for treatment of HCCs since 2014. In the current study, the feasibility and the issue of multipolar LRA were assessed by short-term therapeutic results.

Methods: We performed LRA under general anesthesia in patients with HCCs ≤ 4 cm in diameter and ≤ 3 nodules. RFA needle applicator was inserted under laparoscopic ultrasonography guidance, regardless of tumor location. In case of tumor on hepatic surface or subdiaphragmatic lesion, LRA can be performed safely by maintaining a sufficient fluid space between the target lesion and other organs for avoiding thermal damage to adjacent organs. It aimed at the parallel insertions based on dosimetry table and no-touch ablation as much as possible in multipolar LRA.

Results: Fifty-three patients with a mean age of 69.1 years with 90 HCCs were treated by multipolar LRA. The maximum diameter of the tumors averaged 22.7 ± 6.3 mm (10–42). The average time of follow-up was 6.0 months (0.5–15.2). In all cases, sufficient ablated area as planned was obtained, and there was no local recurrence and mortality. On the other hand, despite performing needle tract cauterization, bleeding was observed in 51% in early period. The bleeding

rate is three times that of using monopolar RFA needle (Cool-tip; COVIDIEN, USA) ($P < 0.01$). On the occasion of bleeding, complete hemostasis was achieved by treating with coagulation forceps. After modification of tract cauterization method, bleeding rate decreased. All patients were discharged without valiance of clinical pathway.

Conclusions: The laparoscopic approach offers parallel insertion of multiple applicators without limitation caused by echo window and/or the ribs. Although a short-term results, there was no local recurrence. To attempt at no-touch ablation may lead to obtain a sufficient safety margin. Multipolar LRA is feasible for localized HCC treatment by gaining good ablated area as we planned safely, though there are some issues such as bleeding from needle tract or skills of multiple insertions.

P1-19

Radiofrequency Ablation in Very Elderly Patients with Liver Tumors

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Background: Hepatocellular carcinoma (HCC) increases in elderly patients. In Japan, the treatment result of HCC is good. Therefore, the age of HCC patients may become older. Some cases are often seen that very elderly patients (VEP: 85 years old or older) are not targeted for positive treatment of HCC because of reduced hepatic function, hypertension, diabetes, dyslipidemia, and functional disorders of other organs.

Aim: Choosing Radiofrequency Ablation (RFA) in very elderly patients with HCCs must be decided by considering radicality and tolerability. We aimed to evaluate the safety and efficacy of RFA in VEP in this study.

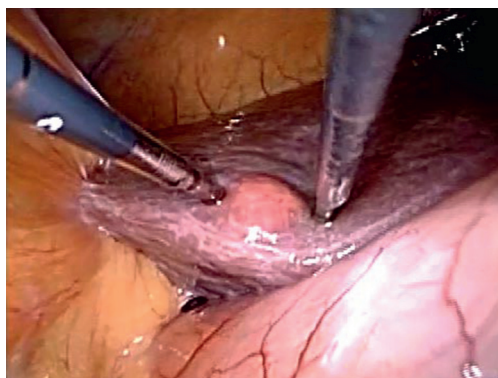


Fig. 1. (for Abstract P1-18).

Methods: Patients were 34 VEP who underwent RFA between December 2012 and November 2014 at our institute. We investigated the rate of cases which were beyond the general indication of RFA, 3 or fewer nodules, all 3 cm or less in diameter, the rate of complications, technical success (It was defined that complete ablation of the tumor was demonstrated by contrast-enhanced CT scan) rate, and 1-year survival.

Results: A total of 55 RFA treatments were performed in 34 VEP. In 30 HCC patients, 8 of 45 treatments (18%) were beyond the general indication. Grade II complications occurred in 1 of 45 (intraoperative bleeding required blood transfusion). Technical success rate was 100% and 1-year survival was 90% (9 of 10 patients, 1 patient died of HCC). In 4 metastatic liver cancer patients, 3 of 8 treatments (38%) were beyond the general indication. Complications did not occur. Technical success rate was 100% and 1-year survival was 100% (3 of 3).

Conclusions: RFA was performed safely in VEP. Short-term efficacy judged by technical success rates and 1-year survival was satisfactory, although there were many patients beyond the general indication of RFA. RFA may be a treatment of choice in VEP not only with HCC but also with metastatic liver tumors.

P1-20

Recurrence and Prognosis Factors of RFA for Primary HCC

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Background: Radiofrequency ablation (RFA) has been widely performed on patients with early-stage hepatocellular carcinoma (HCC), three or fewer tumors each 3 cm or less in diameter as first-line treatment. However, prognosis of patients who received RFA for primary HCC after curative treatment has not been fully evaluated. The aim of this study is to evaluate recurrence, prognosis and associated factors after RFA as an initial therapy for primary HCC in a single center.

Methods: Between January 2003 and December 2013, 162 primary HCC patients were underwent RFA treatment at our institute. We analyzed the outcome in patients with HCC less than 3 cm and 3 nodules with HCV- or HBV-related liver diseases. Recurrence and survival were described with the Kaplan-Meier method. Cox proportional hazard models were used to predict independent covariates associated with overall survival (OS) and recurrence-free survival (RFS).

Results: We studied 162 patients (male: n = 99 (61.1%), female: n = 63 (38.9%)) and mean age was 69 years ranging from 39 to 89 years old. Average follow-up time was 54.5

months. Child-Pugh scores of A/B were 117 (72.2%)/45 (27.8%). HCC stages of 0/A as defined by the Barcelona Clinic Liver Cancer (BCLC) Staging System were 62 (38.3%)/100 (61.7%). One hundred forty five (89.5%) patients had HCV-related HCC and 17 (10.5%) patients had HBV-related HCC. One hundred sixteen (71.6%) patients had single nodules. Average tumor diameter was 1.86 cm. Estimated cumulative overall survival rates at 5 years was 68.9%. Univariate analysis showed that OS was associated with Child-Pugh class A ($p < 0.001$), BCLC stage 0 ($p < 0.05$), age (< 75 years) ($p < 0.05$), higher level of platelet ($p < 0.001$), higher level of prothrombin time ($p < 0.01$), higher level of albumin ($p < 0.001$), lower total bilirubin ($p < 0.001$), lower baseline AFP (< 10 ng/dl), and lower baseline PIVKA-II (100 mAU/ml) ($p < 0.001$). Multivariate analysis identified higher level of platelet, lower baseline PIVKA-II (100 mAU/ml) and age (< 75 years) as independent predictors of death. The 1-, 2-, 3-, 5-year recurrence rate after successful RFA in 158 patients with primary HCC were 31.7/55.7/70.0/82.5%, respectively. Univariate analysis showed that RFS was associated with lower baseline AFP level (< 40 ng/ml), single nodule, BCLC stage 0 ($p < 0.05$), lower level of BMI (< 25) ($p < 0.05$), administration of branched-chain amino acid (BCAA) ($p < 0.05$), and lower level of AST ($p < 0.01$)/ALT ($p < 0.05$)/ γ -GTP ($p < 0.05$). Multivariate analysis showed that lower baseline AST level (< 80 IU/ml), lower level of BMI and BCLC 0 were independent predictors of recurrent free survival after successful RFA for primary HCC.

Conclusions: Higher platelet, lower baseline PIVKA-II, and younger age (< 75 years) were independent predictors of OS after initial RFA therapy for the primary HCC. Lower baseline AST level, lower BMI and BCLC 0 had impact on early recurrence even after successful RFA for the primary HCC.

P1-21

Local Recurrence in the Tumor Blood Drainage Area After Radio Frequency Ablation

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Background: Local tumor recurrence after radiofrequency ablation occurs due to untreated satellite lesions. Satellite lesions in the blood drainage area of the tumor have been reported. Corona enhancement has recently been proposed to represent the blood drainage area. This prospective cohort study evaluated the frequency of intrahe-

patic metastases within the blood drainage area depicted on computed tomography (CT).

Methods: Participants comprised 364 consecutive patients enrolled between April 2002 and December 2011. Participants were divided into two groups according to whether the ablation area covered the entire blood drainage area as defined by delayed-phase CT during hepatic arteriography (Group A) or not (Group B). Local tumor progression and survival rates were compared between groups.

Results: Median time to recurrence was significantly shorter for Group B (434 days) than for Group A (1474 days, $P = 0.0037$). Cumulative local recurrence rates for Group A were 0%, 0%, and 1.5% at 1, 3, and 5 years postoperatively, respectively. In comparison, rates for Group B were 3.8%, 17.0%, and 22.8%, respectively ($P < 0.0001$). Cumulative survival rates were 77.8% and 57.0% at 3 and 5 years, respectively, for Group A. Cumulative survival rates tended to be lower in cases with recurrence in the drainage area ($P = 0.0519$), at 72.5% at 3 years and 34.9% at 5 years.

Conclusion: The safety margin for radiofrequency ablation should be defined as the blood drainage area. Ablation should aim at acquiring adequate safety margins.

P1-22

Verification of the Accuracy of a Needle Tracking System for Use with Bipolar Radiofrequency Ablation Electrodes

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Background: It is often difficult to recognize the exact needle tip location on US images. A needle tracking system helps to identify the needle tip via US imaging. The purpose of this study was to assess the accuracy and efficacy of a needle tracking system in both phantom and clinical studies by utilization of bipolar radiofrequency ablation (RFA) electrodes.

Methods: To better visualize the tip of the electrode, we used a needle tracking system in conjunction with a volume navigation system. In the abdominal biopsy phantom, the angles of the puncture lines were 22.9°, 29.0°, and 36.6° using the convex probe and 39.0° using the micro-convex probe. The punctures were performed twenty times at each puncture angle, respectively. In the clinical study, 21 patients with nodules close to an extrahepatic organ or a major vessel were enrolled between May 2014 and October 2014. After puncture with the needle tracking system, computed tomography (CT) was then performed while the electrode was still within the patient's liver. The distance was measured between the tip of electrode and the closet edge of extrahepatic organ or major

vessel on both B mode US and CT. By comparing these distances, the accuracy of this system was evaluated.

Results: In the phantom study, the deviation between the tip of electrode and the virtual tip of the electrode was analyzed. The 36.6°-puncture line was significantly deviated than other angles (10 vs. 36.6°, $P < 0.001$; 22.9 vs. 36.6°, $P < 0.001$; 29° vs. 36.6°, $P < 0.001$). The median values were within 2 mm at each puncture angle. In the clinical study, 21 nodules in 21 patients were treated. Median tumor diameter was 15.3 ± 7.2 mm. The nearby extrahepatic organs and major vessels were as follows: colon, 3; heart, 11; inferior vena cava, 3; and major portal vein, 4, respectively. The median distance measured between the tip of the electrode and extrahepatic organ on B-scan US was 20.8 ± 1.9 mm, while that on CT was 21.9 ± 1.8 mm ($P = 0.995$). All nodules were completely ablated. Severe complications did not occur.

Conclusions: We can successfully treat high-risk nodules near major vessels or other extrahepatic organs using this system with a bipolar electrode.

P1-23

Complete Ablation of a Single Liver Surface Hepatocellular Carcinoma with Laparoscopic RFA: A Case Report and Literature Review

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Background: Tumors at high-risk locations may limit the effects by percutaneous RFA, some patients may need other alternative methods to get complete ablation.

Methods: A case report and literature review.

Results: A 69-year-old patient with non-viral hepatitis related cirrhosis was referred to our hospital. A MDCT scan confirmed a single capsular tumor (4.5 cm x 4.9 cm x 4.1 cm) of segment IV with wash-in in arterial phase and wash-out in delay phase. A Liver biopsy confirmed the diagnosis of HCC. Blood tests showed normal AFP level and Child-Pugh class B cirrhosis. The TACE was performed and a follow-up CT scan revealed residual tumor. The percutaneous RFA (PRFA) was provided to the residual HCC, combined with artificial ascites method. The 2nd CT scan confirmed small survival lesion. In the 2nd RFA session, in order to achieve complete ablation, we performed combinations of artificial ascites and PEI with technical success. The Gd-EOB-DTPA-MRI confirmed the same residual lesion. We considered laparoscopic RFA was effective for the lesion unable to ablate completely with PRFA. Under laparoscopy, the tumor was on liver surface, we inserted the RFA electrode directly, and removed the electrode after 3 times ablations without complications.

Conclusion: The efficacy of RFA depends on tumor locations. Liver surface tumor may be not easy to ablate under

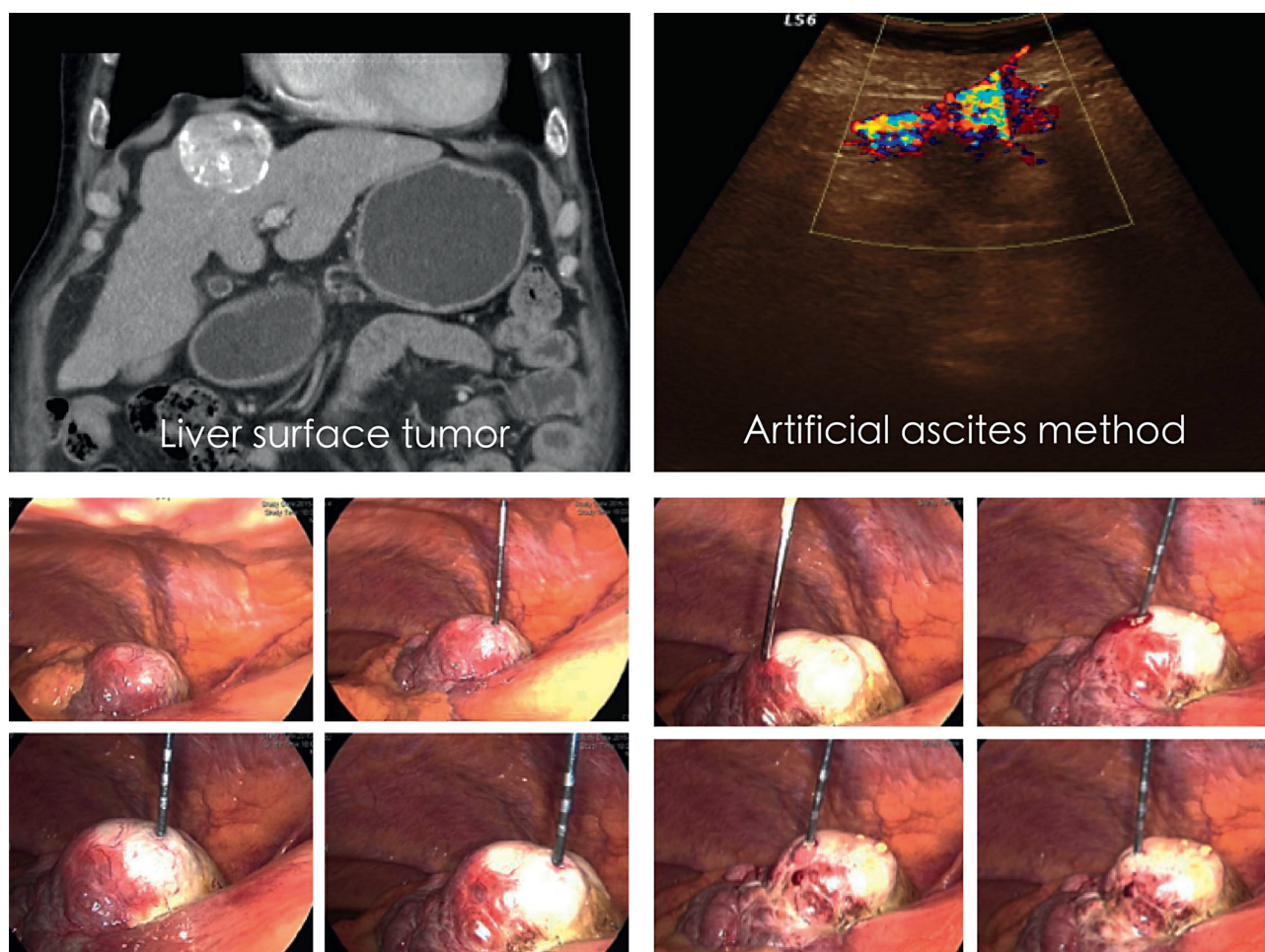


Fig. 1. (for Abstract P1-23).

PRFA because of the needle insertion angle may be restricted by the ribs, air, or less optimal positioning of the RFA electrode [1]. A study mentions that HCC nodules adjacent to liver surface show higher recurrence than others [2]. Hence, several alternative methods under RFA were developed to get higher complete ablation rate. Artificial ascites method has been reported. Although this method can easily perform, complete ablations may not be properly carried out in all cases. A study analysis 208 HCC tumors management and conclude a higher complete ablation rate with the use of RFA and PEI in high risk locations compared with the rate for RFA only [2]. Moreover, the laparoscopic RFA (LRFA) provides the advantages of direct observation of tumors, direct visual control of RFA electrodes insertions, offering sufficient safe space to surrounding tissue, and easily managing bleeding [3]. The disadvantage of LRFA is the invasive nature compared with the PRFA, and the complications of laparoscopy [4]. LRFA maybe a complementary choice for patients with lesions are difficult to perform PRFA.

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P1-24

Safety and Efficacy of Radiofrequency Thermal Ablation for Patients with Liver Tumors After Choledochojunostomy: Our Single Center Experience

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Introduction: Radiofrequency thermal ablation (RFA) for primary or metastatic liver cancer is used worldwide due to its high local tumor control rate with minimal invasiveness if a target tumor is small in size. As increased risk of complications of liver abscess and/or biloma formation after RFA is highly expected especially in patients after choledochojunostomy, such patients are considered to be a relative contraindication for RFA in some institutions. In this report, we investigated the safety and efficacy of RFA for recurrent malignant liver tumors in patients undergoing choledochojunostomy as an initial treatment in our hospital.

Subjects and Method: We have performed a total of 4,526 RFA sessions for 1,689 patients with primary or metastatic liver cancer from June 1999 to the end of December 2012 in our hospital. Of these, 11 patients who underwent RFA for recurrent liver malignant tumors after choledochojunostomy within these periods were included in this study. We examined their clinical background, short-term results, prognosis, RFA related complications and discussed the validity and problems of performing RFA for the case after choledochojunostomy.

Results: The average (range) age of analyzed 11 patients are 72 (51–83) years old. They included 10 male and one female. A total of 14 sessions of percutaneous RFA were underwent for 14 nodules of primary or metastatic liver cancer (mean diameter, 2.2 cm). The diagnoses of the target liver tumors are: three nodules in 3 patients with hepatocellular carcinoma (HCC) and 11 nodules in 8 patients with metastatic liver cancer (pancreatic cancer, 9 nodules in 2 patients; bile duct cancer, 2 nodules in 2 patients). Of 11 patients, we experienced RFA related biloma or liver abscess in three patients (27.2%), which needed some interventions after RFA. Herein, we present one of these three cases. A 75 years old man with HCC. He underwent pancreaticoduodenectomy for duodenum papilla cancer and anterior segment liver resection for HCC. Recurrent nodule of HCC of 2 cm in diameter located adjacent to the bifurcation between anterior and posterior branch of the right portal vein was diagnosed and RFA was

performed. Biloma developed in segment 8 approximately 40 days after RFA. The biloma rapidly progressed, perforated to thoracic cavity, and resulted in forming a refractory choledochobronchial fistula.

Discussion: Recurrent liver tumors after choledochojunostomy have been regarded as tumors easy to be complicated by biloma and/or liver abscess after RFA owing to the contaminated bile ducts. When we plan to perform RFA in such patients, we should evaluate its indication fully considering risks and benefits in the individual case, and enough informed consent for each patient should be needed. The probability of developing RFA related complications is partly depending on the site of target tumor. RFA therapy for the nodule near the proximal portal vein branch (segmental or main portal vein branch) should be avoided because of its highly expected complications. Whereas tumor nodule located near the liver surface would be a good candidate for RFA due to its safe procedure.

Conclusions: Although the patients after choledochojunostomy tend to be complicated by biloma and/or liver abscess after RFA, in some strictly selected patients, RFA can be a treatment option. However, devise to minimize the ablative margin of RFA for preventing complications may be necessary even in those cases.

P1-25

Survival Analysis of Re-Resection Versus Re-Radiofrequency Ablation for Intrahepatic Recurrence After Initial Hepatectomy or Radiofrequency Ablation for Hepatocellular Carcinoma: 10-Year Experience

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Background & Aims: Hepatic resection and radiofrequency ablation (RFA) have been suggested as curative treatment options for treating hepatocellular carcinoma (HCC) in the current guideline. In patients with initial HCC of the

Barcelona Clinic Liver Cancer (BCLC) stage 0 or A, survival outcomes of resection and RFA were not significantly different. However, in patients with recurrent HCC, survival of patients treated with re-resection has not been compared with those with re-RFA. This study aimed to compare survival of patient treated with re-resection to those with re-RFA in patients with BCLC 0/A.

Methods: This retrospective study included 225 consecutive patients who all recurred BCLC 0/A HCC in Child-Pugh class A/B. The patients were treated with resection or RFA for initial or recurrent HCCs. According to initial treatment strategies, patients were divided into two groups; 148 patients treated with RFA and 77 patients with resection. For treating recurrent HCC, patients were also divided into two different treatments: 181 patients treated with RFA and 44 patients with resection. The survival rates comparing each group according to treatment strategies were analyzed after matching of propensity scores: liver cirrhosis or HCC risk factors.

Results: The median MELD score was 7.0 and 7.0; the median tumor size was 2.4 cm and 1.5 cm; single HCC was 80.9% and 84.9%; the median alpha-fetoprotein level was 11.3 and 7.4 ng/ml in patients with initial and recurrent HCC, respectively. The median observed duration was 5.74, 3.81, 5.34, and 4.43 years; the 5-year overall survival rates were 85.3%, 93.0%, 89.5% and 95.0% in patients treated with resection for both initial and recurrent HCC, RFA for initial HCC and resection for recurrent HCC, resection for initial HCC and RFA for recurrent HCC, and RFA for both initial and recurrent HCC, respectively. In patients treated with RFA for initial HCC, survival rates were not significantly different according to second treatment strategies such as RFA or resection for recurrent HCC ($P = 0.277$); in patients who received resection for initial HCC, survival rates also did not show significant difference according to second treatment strategies ($P = 0.177$). Survival rates in patients treated with resection for initial and RFA for recurrent HCCs were not significantly different from those with RFA for both initial and recurrent HCCs ($P = 0.234$), and those with RFA for initial HCC and resection for recurrent HCC ($P = 0.655$). Patients treated with resection for both initial and recurrent HCCs showed significantly lower mortality than those with RFA for initial and recurrent HCCs; hazard ratio of 0.143 (95% confidence interval, 0.021–0.991, $P < 0.05$). In subgroup analysis, patients who received resection at least for initial or recurrent HCC showed lower mortality than those who only treated with RFA for initial and recurrent HCC; hazard ratio of 0.414 (95% confidence interval, 0.187–0.913, $P = 0.029$).

Conclusions: In patients with initial BCLC stage 0 or A, and early cirrhosis, who recurred HCC with BCLC stage 0 or A, re-hepatectomy improves the patient survival compared to those treated with re-RFA treatment. Treatments including resection for initial or recurrent HCC with BCLC stage 0/A also improves the survival when compared to RFA only treatment. Therefore, for selected patients, re-hepatectomy should be considered as the first treatment option for initial and recurrent HCC.

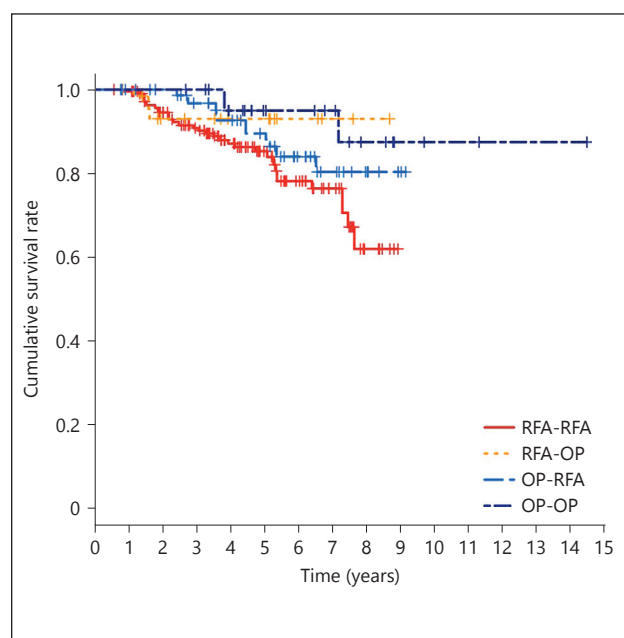


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P1-26

Withdrawn

P1-27

Current Status of Radiofrequency Ablation in Western Japan – The Questionnaire Survey at the 8th Meeting of Chugoku-Shikoku Liver Cancer Local Ablation Therapy Study Group

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Backgrounds: Radiofrequency ablation (RFA) is one of the most important treatment modality for Hepatocellular carcinoma (HCC). The aim of this study is to reveal the changes of RFA in the last decade in Japan.

Methods: We examined the current status of RFA by questionnaire survey in major 27 hospitals performing RFA in Chugoku-Shikoku district, and compared to the results of the similar questionnaire conducted 10 years ago.

Results: In 2013, 2130 patients were treated by RFA. Complications were observed in 25 cases (1.2%). Fifty percent (13/26) of the hospitals considered that inclusion criteria for RFA was less than or equal to 3 nodules, and 60% (16/26)

considered that the criteria was nodules within 30 mm in diameter. RFA was performed even in BCLC-B patients in 19 (70.4%) hospitals. Bipolar RFA system was adopted in 17 (59.3%) hospitals; however, it was controversial whether bipolar would be the first choice in the future. RFA for HCC located in caudate lobe was performed in 18 (66.7%) hospitals, and 4 hospitals experienced more than 30 cases to date. Fixed ablation time was adopted in most of the hospitals 10 years ago (8/26), but the recent trend was to determine the ablation time based on the extent of microbubble during the procedure observed by ultrasonography (8/26). Ten years ago, only our hospital put the grounding pad in back, however, the procedure was expanded to 5 hospitals now. Hospitals using navigation system (2→16) and the puncture under the contrast-enhanced ultrasonography (3→22) are markedly increased compared to 10 years ago. The artificial pleural effusion or ascites methods were increased from a decade ago (18/26), and were currently used in most hospitals (25/26). Cooling of bile duct by endoscopic nasobiliary drainage tube during RFA was performed in 5 hospitals (19.2%) 10 years ago and the number of hospitals using this technique increased to 10 (38.5%). The Grisons anesthesia for the prevention of vagotonia and pain during RFA was developed several years ago and currently 3 (13%) hospitals performed it.

Conclusion: Compared to 10 years ago, many hospitals have employed various devices and techniques for RFA. RFA in Japan has certainly evolved, and is expected to develop in future.

P1-28

Neutrophil/Lymphocyte Ratio Does Not Predict the Recurrence After Curative Treatment with Radiofrequency Ablation for Small Hepatocellular Carcinoma

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Background: Radiofrequency ablation (RFA) is an established treatment for small hepatocellular carcinoma (HCC). However, the recurrence of HCC is frequently found after curative treatment. Therefore, the prevention of recurrence is essential for long survival in patients with HCC. On the other hand, neutrophil/lymphocyte ratio (NLR) has been reported to be the prognostic factor of HCC. In this time, we analyzed the factor that influenced the recurrence and survival after curative RFA for HCC.

Methods: HCC cases who had been initially treated with RFA from 2003 to 2014 were analyzed retrospectively in this study. Liver function, tumor factor (tumor marker, tumor size, number) and general condition (diabetes mellitus, anti-viral treatment, NLR) were evaluated in these cases. Furthermore

recurrence free survival (TTP) and overall survival (OS) were analyzed, and associated factors were assessed.

Results: 163 patients with HCC were treated with RFA. Median age was 71.5 years old, male was dominant (M:F = 6:4), and most were Child A (129 cases, 79.1%). As the etiology of liver disease, HCV was most prevalent (111 cases, 68.1%). Median NLR was 1.7 in these cases. The mean size of HCC was 19 mm and the average number was 1.4/case. During median follow-up of 44 months, the recurrence of HCC (both intrahepatic distant recurrence (IDR) and local recurrence (LR)) was found in 101 cases (61.9%). Among the recurrence, LR was found in 11 cases (6.7%), most of the recurrence was IDR. Median TTP was 31 months, and median OS was 75 months. The strongest factor associated with OS was the presence of the recurrence in this study (hazard ratio 4.65, $p = 0.01$). When we assessed factors associated with the recurrence, male, diabetes mellitus, AFP >100 ng/ml, DCP >40 mAU/ml and anti-viral treatment were indicated, but NLR was not associated with the recurrence.

Discussion: NLR was reported to be associated with intra-tumor macrophages, and therefore small HCC may not be suitable for the NLR assessment due to the small volume of tumor.

Conclusion: To obtain longer survival after curative treatment with RFA for small HCC, the prevention of IDR is essential. The management of diabetes mellitus and anti-viral treatment may be important for patients with HCC to prevent IDR.

P1-29

Radiofrequency Ablation for Hepatocellular Carcinoma Which Performed with Affixing Return Electrode to a Back

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Introduction: Radio Frequency Ablation (RFA) has been performed as a main treatment for hepatocellular carcinoma (HCC). It is recommended to attach a return electrode on the patient's thigh at the time of treatment. There is a report of shortening the ablation time when a return electrode has been attached to the back of patients. In this study, we examined the effects to conduct our report.

Method: The subjects were 79 patients in which a return electrode was attached to their backs and ablated with a single pulse during the period from mid-June 2014 until February 2015 (A group) and 52 patients in which a return electrode was attached to their thigh as unconventionally done during the period until early June 2014 (Group B) for comparison.

Group A: Male/Female cases were 53/25, average age was 72.1 (52–89) years of age and the cases of background liver; HCV/HBV/NBNC were 55/8/14 cases.

Group B: Male/Female cases were 32/21, average age was 70.9 (45–86) years of age and the cases of background liver; HCV/HBV/NBNC were 32/12/9 (overlapping) case. We analyzed the following: the time required to complete ablation, final temperature reached, major diameter of maximum ablation, presence of complications and patients' medical history. We used the Cool-tip RFA system (Valleylab Inc.) as a RFA generator, attached a return electrode on the patients' backs and performed ablation in impedance mode. We increased a 2 cm needle output level by 10 W per minute starting at 40 W. We increased a 3 cm needle output level by 20 W per minute starting at 60 W. As for ablation time, regardless of the roll-off times, we continued the ablation until therapeutic effects were thought to be sufficient based on the imaging.

Results: In Group A, the average ablation time was 248.1 seconds with a 2 cm needle, 259.2 seconds with a 3 cm needle. The average temperature finally reached was 78.5 with a 2 cm needle, and 80.1°C with a 3 cm needle. The average maximum ablation major diameter was 29.4 mm with a 2 cm needle and 44.3 mm with a 3 cm needle. No serious complications were observed. In Group B, average ablation time was 353.6 seconds with a 2 cm needle and 364.0 seconds with a 3 cm needle; thus, ablation time was longer than that in the case where a patch was attached to the back.

Discussion: It was shown that the treatment time can be shortened when a return electrode is attached to the back of patients. We think that we can possibly reduce the patients' pain by reducing the ablation time.

P1-30

One – Step Method in Creating Artificial Ascites for Hepatoma in Difficult Location

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Background: The study aims to improve the success rate and rapidly in creating artificial ascites for treatment of hepatomas located subcapsularly or in difficult location.

Methods: 130 consecutive hepatoma patients who required artificial ascites for better visualization or protection from organ injury were recruited between Nov 2011 and Jun 2014. Initial 95 patients were using Seldinger technique to place angiosheath with the remaining 35 patients using one step method. The proportions of patients who had undergone surgery, transarterial chemoembolization or radiofrequency ablation therapy for hepatoma before the procedure were

11% (11/95), 3% (3/95), 37% (35/95) in Seldinger group and 16% (6/35), 0%, 50% (18/35) in one step group, respectively.

Results: The rates for complete success, partial success and failure for Seldinger technique and one step method were 76.8% (73/95), 11.6% (11/95), 11.6% (11/95) and 77.1% (27/35), 20% (7/35), 2.9% (1/35), respectively. The time required from starting the procedure to successful intraperitoneal instillation of glucose water was 3 minutes 20 seconds with one step method, which is marginally shorter than that of 3 minutes 58 seconds with Seldinger technique ($P = 0.058$). The success rates in both groups in previously treated patients were not significantly different.

Conclusion: One step method is as efficient as Seldinger technique in creating artificial ascites yet more time saving.

P1-31

Usefulness of Real-Time Virtual Sonography System to Evaluate Effects Therapeutic RFA for HCC

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Introduction: Studies to evaluate the tumor vascularity in HCC have been done extensively with various imaging modalities because the finding of the vascularity is helpful to evaluate the biological features of the tumor. In the present study, we investigated whether real-time virtual sonography system is useful to display the accurate position of percutaneous radiofrequency ablation (RFA) needle in the tumor and evaluated the efficacy of RFA therapy in patients with HCC.

Materials and Methods: 52 patients with 58 HCC lesions (30 men and 22 women, aged 40 to 90 years with a mean age of 65.9 years), admitted to our Masuko Memorial Hospital between November 2011 and February 2014 were enrolled to the present study. Their diagnosis was confirmed by dynamic CT and celiac angiography. Based on Child-Pugh score, 48 patients was diagnosed as grade A, and 4 patients as grade B. All patients enrolled showed hypervascular enhancement of HCC on contrast-enhanced US and/or dynamic CT. The diameters of tumors were 1.1–2.0 cm in 24 nodules, 2.1–3.0 cm in 19, 3.1–5.0 cm in 9, respectively. All patients gave written informed consent and this protocol had been approved by the Human Studies Committee at Masuko Memorial Hospital. US imaging We used APLIO XG (Toshiba Medical Systems) for RFA therapy with a convex probe and micro-convex-probe as US system. Our solutions is realtime virtual ultrasound (Fusion Imaging)-assisted ablation. Fusion Imaging is a system to depict a CT/MR/US reconstructed imaging of the same slice as that of the ultrasound imaging in real time from a CT/MR/US volume data. We used a radiofrequency generator with 200 W

power connected to a 17-gauge perfusion needle (Radionics Inc., Burlington, MA); the circuit was closed through a dispersive electrode.

Results: It was possible to obtain accurate position of cool-tip needle and to perform RFA procedure in all 52 HCC patients with 58 nodules Fusion Imaging. The simultaneous study before RFA therapy showed the inflow of arterial blood and tumor stain. And importantly it appeared that real-time virtual sonography provided much perceptible information on the spatial relationship between RFA needle and the target lesion, and resulted in accurate therapeutic efficacy for percutaneous RFA procedure.

Conclusion: We experienced the treatment of 58 patient with HCC by RFA using Fusion Imaging. The real-time virtual sonography system is useful for the accurate treatment of HCC with safety, in particular at the time of percutaneous loco-regional procedures.

P1-32

US-US Fusion Imaging in Radiofrequency Ablation Therapy for Hepatocellular Carcinoma

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Backgrounds: It is often difficult to assess the ablation margin of radiofrequency ablation (RFA) therapy on ultrasonography (US). Therefore, contrast-enhanced CT or MRI is widely performed a few days after RFA for early treatment response assessment in Japan. In contrast, US-US fusion imaging can display the synchronous images of before/after RFA side-by-side according to the US probe action, and ablation margin of RFA might be evaluated three-dimensionally immediately after RFA.

Aim: This study investigated the effectiveness of US-US fusion imaging in RFA for HCC.

Materials and Methods: Between July 2014 and February 2015, 27 patients (19 men, 8 women) with 31 hypervascular HCCs were enrolled. Before ablation, three dimensional volume data of US were obtained by sweep scanning, and we traced the edge of HCC for coloring the entire tumor on the data. After ablation, a hyperechoic area was seen on B-mode US. US-US fusion imaging showed the synchronous images of before/after RFA side-by-side after images registration. Moreover, an overlay of US images before/after RFA could reveal an ablation margin three-dimensionally by showing the colored tumor inside hyperechoic area.

Results: The maximal diameters of all tumors ranged from 0.7 to 1.8 cm (mean, 1.3 cm) on US. Complete tumor necrosis was achieved by a single session of RF ablation in all patients. We did not encounter local tumor progression and severe complication during the observation period.

Conclusion: US-US fusion imaging in RFA is an efficient approach for HCCs, and have potential to cancel early CT/MRI assessment of treatment response if ablation margin could be accurately evaluated by US-US fusion imaging immediately after RFA.

P1-33

Safety of DEB-TACE for the Treatment of Hepatocellular Carcinoma: A Single Center Experience

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Background: Drug eluting beads chemoembolization (DEB-TACE) has been reported to be as effective and safe as conventional TACE. We aimed to confirm the safeness of DEB-TACE.

Methods: A total of 39 sessions of DEB-TACE were performed in 24 patients (20 men and 4 women; median age, 76 years old; 13 cases with HCV infection, 8 cases with diabetes mellitus, and 3 cases with alcoholic liver cirrhosis). We used either DC bead® (100–300 µm) loaded with epirubicin (20 sessions) or HepaSphere™ Microspheres (50–100 µm) loaded with cisplatin (19 sessions). Adverse events and change in Child-Pugh score after DEB-TACE were evaluated. Continuous variables were expressed as the median (inter-quartile range).

Results: The size of largest tumor was 2.7 (1.8–3.9) cm; the number of nodule was 2 (1.5–6). To treat them, 0.3 (0.2–0.6) vial of DC bead® or HepaSphere™ was infused. Grade 1–2 elevation in ALT was observed in 13 sessions and grade 3 in 1 session. High fever was observed in 10 sessions, and low-grade fever in 6 sessions. A case died of pneumonia 1 week after treatment and a case died of disease progression 1 month after treatment. Child-Pugh score was evaluated 1–3 months after treatment in 29 sessions. It increased in 7 sessions (24%) and decreased in 9 sessions (31%).

Conclusions: DEB-TACE was generally safe and not likely to worsen liver function in most cases; however, careful selection of cases to treat should be considered.

P1-34

Does Multiple TACE Session Affect Survival and Side Effects

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Background: Hepatocellular carcinoma is one of the commonest cancers in the world with a predilection towards Asian populations. Many cases at presentation are non resectable and limitation of donors make liver transplantation unreachable for many. Transarterial chemo embolization (TACE) and selective internal radiation therapy (SIRT) are two options in management of unresectable HCC but their side effects have a significant influence on continuation of treatment. In this study we look as side effect profile of TACE and how multiple episodes of TACE influence side effects and survival of the patients.

Methods: A retrospective study was carried out and 306 TACE sessions in 149 patients done from 2001 to 2013 were included in the study. Patient cohort was divided into two groups. First group is where patients underwent 3 or less TACE sessions. The other group is where patients underwent more than 3 TACE sessions.

Results: The most common post TACE side effect was fever occurring in 96 (26.2%) instances. The group undergoing less than three TACE sessions showed a complication rate of 37% while the group undergoing more than 3 TACE sessions showed a complication rate of 57%. Average survival of the patients after a TACE session was 16.88 months. There were 9 cases of TACE related mortality out of which 8 cases occurred in patients undergoing less than 3 sessions of TACE.

Only a single TACE related death was reported in patients undergoing more than 3 sessions.

Discussion: A higher number of TACE sessions are associated with a higher rate of complications, which increases with each subsequent episode of TACE and approaches almost 100% by the 7th session. No significant higher risk of mortality was found associated with multiple TACE sessions. Proper patient selection can minimize side effects associated with TACE and increase patient tolerability.

P1-35

Predictors of Complete Response in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization

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Background/Aims: Transarterial chemoembolization (TACE) is the recommended treatment for patients with Barcelona stage B hepatocellular carcinoma (HCC); however, community practice varies from these American Association for the Study of Liver Diseases guidelines. The aim of this study is to assess factors determining initial response and prognostic factors after repeated TACE for HCC.

Methods: From January 2013 to December 2013, 184 patients with newly diagnosed HCC were treated at the Chang Gung Memorial Hospital, Linkou Medical Center, 98 patients underwent TACE with on-demand treatment policy (Figure 1). According to modified Response Evaluation Criteria in

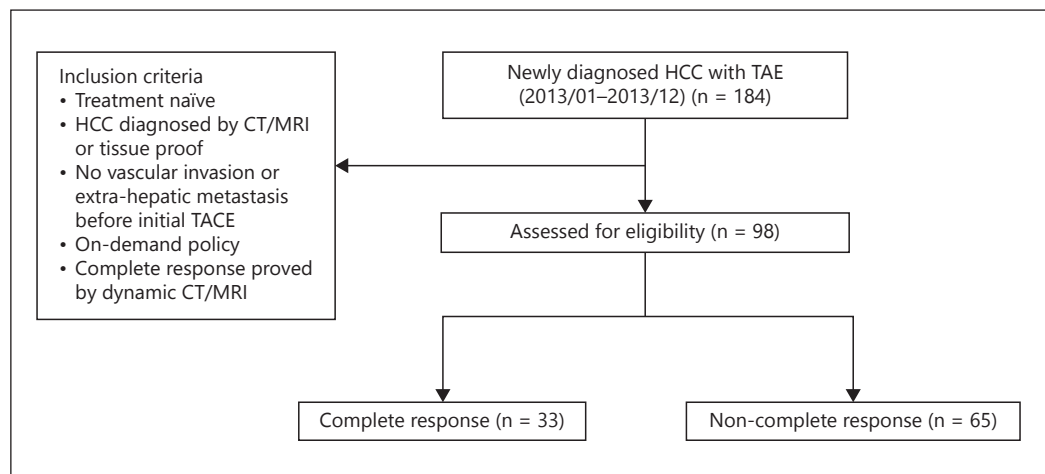


Fig. 1. Flowchart of patients selection in the study (for Abstract P1-35).

Solid Tumors (mRECIST) guideline, we categorized patient as four groups: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The primary outcome was CR after series of TACE whether conventional method or drug-eluting bead (DC-BEAD®). The results are expressed as median (range) values. Categorical variables were analyzed with a Pearson's chi-square test. Non-categorical variables were compared with independent t-test. Logistic regression analysis was applied for predictors of mortality within six weeks. All tests were two-tailed, and the level of statistical significance was set as $P < 0.05$. Analysis was performed with SPSS V.20 (IBM, USA).

Results: The mean age of the 98 patients was 65.3 years, 71.4% were males and 87.8% had chronic virus (HBV or HCV) infection. The median size of the largest target lesion was 3.9 cm, median numbers were 2 tumors and 32.7% were multifocal. Twenty-two patients died after mean 253 days from the initial TACE treatment. Mean overall survival from initial TACE was 15.2 months. Multifocal tumors invasion (OR: 0.001, 95% CI: 0.017–0.341, $p = 0.049$), response to initial TACE (OR: 21.33, 95% CI: 2.743–165.93, $p = 0.003$), within Milan criteria (OR: 9.524, 95% CI: 3.257–27.78, $p < 0.001$), and serum albumin level (OR: 2.407, 95% CI: 1.140–5.081, $p = 0.021$) were significant by univariate analysis. By multivariate analysis, response to initial TACE (OR: 14.92, 95% CI: 1.733–128.36, $p = 0.014$) and within Milan criteria (OR: 5.650, 95% CI: 1.582–20.41, $p = 0.008$) appeared to be predictors of approaching final CR after repeated TACE.

Conclusion: In our study, response to initial TACE and within Milan criteria played important roles in determining CR. Further larger populations are required to validate our findings.

P1-36

Predicting Factors of Complete Response After Transarterial Chemoembolization in HCC

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Background: Transarterial chemoembolization (TACE) is a common intervention performed for hepatocellular carcinoma (HCC). The aim of this study is to evaluate prognostic factor of the initial complete response during first TACE for HCC.

Methods: We retrospectively reviewed a total of 93 patients who diagnosed as HCC and performed the first TACE in our institution. Tumor response was estimated based on the result of computed tomography after TACE.

Results: Thirty-five patients (37.6%) patients have no need for repeat TACE in 6 months. Mean number and size of

HCC was 2.5 and 2.1 cm of complete response patients. Mean AFP level was 168 ng/dl. Complete response rate was 52.6% in HCC size < 2 cm. More than 3 cm, 4 cm, and 5 cm HCC has 25%, 12.5%, and 0% complete response rate. Complete response was 45.7% (21/46), 31.3% (5/16), 33.3% (2/6) for the patients with one, two, and three HCCs, respectively. Patient with complete response as initial response have small HCC and small number of HCC. Measures of liver function and TACE approach were not predictive of complete response.

Conclusion: TACE would be a curative treatment option for small size and small number of HCC.

P1-37

Neoadjuvant Transcatheter Arterial Chemoembolization Does Not Provide Survival Benefit Compared with Curative Therapy Alone in Single Hepatocellular Carcinoma

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Background: Transcatheter arterial chemoembolization (TACE) can reduce tumor arterial blood flow, reduce the tumor size and to avoid further tumor cell dissemination. Thus enhance the effects of radiofrequency ablation (RFA) or hepatic resection (HR) and reduce the risk recurrence. On contrary, also reports did not suggested combination have a beneficial effect over surgical resection alone. The study is to clarify whether TACE plus sequential curative therapy provides benefits in single hepatocellular carcinoma (HCC).

Method: A total of 470 HCC during 2005 and 2010 were retrospective analysis from cancer registration. The factors associated with clinical outcomes including gender, age, etiology, Child-Pugh class, BCLC stage, serum alpha-feto protein (AFP) level, tumor size, tumor response and recurrence status and survival period. Overall survival (OS) and Disease free survival (DFS) were analyzed by the Kaplan-Meier actuarial curve method with the log-rank test. The Cox regression hazard model was used to identify the independent predictive factors for OS and DFS.

Result: Of 470 HCC patients, 312 were male and the median age was 63 years old. The median follow up period was 26.6 months. forty% of patients had hepatitis B virus (HBV) infection. The median tumor size was 2.7 cm and the

tumor size was <5 cm in 82.4% of patients. In total, 190 (40.4%) patients received curative therapy, including HR in 125, RFA in 47 and percutaneous ethanol injection (PEI) in 18 patients. The others were TACE alone (44.7%) or TACE plus curative therapy (14.9%). The one-, three- and five-year overall survival (OS) rates of all patients were 92.6%, 73.3% and 59.6%, respectively. Child-Pugh class A ($p < 0.003$), very early stage BCLC ($p = 0.043$), tumor size <5 cm ($p = 0.015$), AFP level <200 ng/ml ($p = 0.001$) and curative-based therapy ($p < 0.001$) were factors associated with better OS. The one-, three- and five-year disease-free survival (DFS) rates of all the patients were 75.4%, 53.7% and 36.3%, respectively. Only Child-Pugh class A ($p = 0.022$) and curative based therapy ($p = 0.006$) were significantly associated with better DFS. The OS and DFS did not showed significant better in neoadjuvant then curative alone according to various parameters, including gender, age, etiology, Child-Pugh class, BCLC stage, tumor size or AFP level. In contrast, TACE plus sequential curative therapy resulted in significantly lower OS in patients of Child-Pugh class A ($p = 0.015$) and BCLC very early stage ($p = 0.002$) and lower DFS in patients of BCLC very early stage ($p = 0.004$).

Conclusion: TACE before sequential curative therapy, including surgery or RFA, did not provide survival or recurrence-free benefits in single HCC. Neoadjuvant TACE should not be recommended in single HCC patients who are indicated for curative therapy.

P1-38

The Clinical Study of Serious Complicated Patients After Transcatheter Arterial Chemoembolization Therapy of Hepatocellular Carcinoma

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Background: Although transcatheter arterial chemoembolization (TACE) has been a major treatment modality for unresectable hepatocellular carcinoma (HCC), a number of complications associated with TACE have been reported in many studies. The aim of this study was to evaluate the clinical characteristics of serious complicated patients after TACE of HCC, except the patients who were recovered within 1 week.

Methods: We reviewed retrospectively clinical characteristics of serious complicated 24 patients, 15 patients who were expired and 11 patients who were hospitalized more than 30 days, from 969 TACE procedures during 5 years in our hospital.

Result: The causes of serious complication were decompensated hepatic failures (12 cases; 50%), tumor ruptures (5

cases; 20.8%), variceal bleedings (3 cases; 12.5%), gastric ulcer bleeding (1 case; 4.2%), slow recovery due to associated with other disease (2 cases; 8.3%), the other cause (1 case; 4.3%). Eleven patients (1.1%) were survived and 15 patients (1.5%) were died among the serious complicated HCC patients after TACE therapy. The severity of liver disease according to the Child-Turcotte-Pugh (CTP) score was related to the patient's survivor (7.45 ± 2.46 vs. 9.47 ± 1.77 ; $P = 0.023$).

Conclusion: The survival rate of decompensated patients after TACE therapy could be improved with intensive supportive care and the more precise prognostic criterias are needed for the safety of TACE therapy of HCC patients.

P1-39

Efficacy of Switching Anticancer Drugs During Conventional Transarterial Chemoembolization for Hepatocellular Carcinoma

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Background: In Japan, the anticancer drugs often used in transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) were epirubicine, cisplatin and miriplatin. Several studies about the short-term effects of each drug and the long-term effects of single agent were reported, but there are few reports about the long-term effects and the prognostic value of changing anticancer agents during TACE therapies. The purpose of this study was to investigate the efficacy of switching chemotherapeutic drugs during TACE sessions for HCC.

Methods: We retrospectively enrolled 65 HCC patients treated with TACE at least more than twice since July 2003 to June 2011. Patients were divided into two groups, group A ($n = 30$): not switching anticancer drug, group B ($n = 35$): switching anticancer drugs. Overall survival time was calculated by the Kaplan-Meier method was compared using log-rank test. The predictive factors of survival were subjected to multivariate analysis using Cox's proportional hazards model.

Results: One year survival rates in group A and group B were 86.7% and 97.1%, and 3 years survival rates were 32.6% and 57.1%, respectively. Median survival time in group A and group B was 2.22 years and 3.23 years, respectively ($p = 0.0283$). Multivariate analysis suggested that switching anticancer drugs, AFP (>20 mg/dl) and hyaluronic acids (>200 ng/l) were independent predictor ($p = 0.0124$).

Conclusion: Overall survival time of HCC patients underwent TACE was significantly prolonged by the change of chemotherapeutic drugs. Switching anticancer drugs during TACE sessions might improve the prognosis of HCC.

P1-40

Efficacy and Safety of Transarterial Chemoembolization Using Drug Eluting Beads for Hepatocellular Carcinoma

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Aim: Transarterial chemoembolization (TACE) using a drug-eluting bead (DEB-TACE) for hepatocellular carcinoma (HCC) is a new treatment method in Japan. In this study we evaluated the efficacy and safety of DEB-TACE for the patients with unresectable hepatocellular carcinoma.

Materials and Methods: 24 patients (M:F = 18:6, age (mean) 68, Child A:B = 18:6, stage II:III:IV = 8:13:3) with unresectable HCC who underwent 44 DEB TACE procedures in 10 months were studied. DEB TACE procedures using Hepa-Sphere eluting CDDP in 27 sessions and DC Bead eluting epirubicin in 17 sessions were performed. The objective radiological response was classified according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 by dynamic CT at one month after therapy. Adverse events were evaluated using NCI CTCAE v. 4.03.

Results: The imaging response was assessed in each session as partial response (PR), stable disease (SD) and progressive disease (PD) in 26 (59.1%), 10 (22.7%), and 8 (18.2%) respectively. In most effective case, huge HCC that was 96 mm in tumor diameter became smaller as 45 mm and also in the tumor marker, AFP decreased from 102.4 to 5.4 and PIVKAI decreased from 31400 to 34 after 3 session of DEB-TACE. As the complication, grade 1 level of pyrexia, vomiting, and abdominal pain were observed in 17%, 6%, and 11% respectively. There was no case in which Child-Pugh score got worse except for the case with PD.

Conclusion: DEB-TACE is safe and effective in achieving local tumor control in patients with unresectable HCC.

P1-41

A Randomized Controlled Study of Effectiveness Between Transcatheter Arterial Chemoembolization with Epirubicin Versus Cisplatin for Multiple Hepatocellular Carcinoma

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Background: In transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), it has not been clarified which chemotherapy agent is an effective combined drug with Lipiodol. We previously showed that Lipiodol-TACE combined with cisplatin (Cis-TACE) provided a higher response rate than Lipiodol-TACE combined with epirubicin (Epi-TACE) for multiple HCC (Hepatol Res. 2011). Here, we conducted a randomized controlled study comparing the effectiveness of Epi-TACE and Cis-TACE.

Method: Sixty patients with multiple HCC which were not indicated for curative liver resection or percutaneous ablation therapy were randomly assigned to Epi-TACE or Cis-TACE group, stratified by the primary or non-primary treatment and the presence or absence of the history of liver resection. The primary endpoint was response rate, and the secondary endpoints were overall survival (OS) and progression free survival (PFS).

Results: Patient characteristics were comparable between the two groups. The response rates were 24.1% for Epi-TACE group and 37.9% for Cis-TACE group ($p = 0.255$). The median OS times were 854 days for Epi-TACE group and 924 days for Cis-TACE group [hazard ratio (HR) for Cis-TACE group against Epi-TACE group: 0.73, 95% confidence interval (CI): 0.37–1.44, $p = 0.364$], and the median PFS times were 117 days for Epi-TACE group and 156 days for Cis-TACE group (HR: 0.78, 95% CI: 0.45–1.32, $p = 0.354$). In subgroup analysis for the stratification factors, response rates of primary treatment were 31.3% for Epi-TACE group and 50.0% for Cis-TACE group ($p = 0.315$), and response rates of non-primary treatment were 15.4% for Epi-TACE group and 29.4% for Cis-TACE group ($p = 0.360$). The median PFS times of primary treatment were 183 days for Epi-TACE group and 166 days for Cis-TACE group (HR: 0.91, 95% CI: 0.41–1.98, $p = 0.814$), and the median PFS times of non-primary treatment were 78 days for Epi-TACE group and 114 days for Cis-TACE group (HR: 0.50, 95% CI: 0.23–1.10, $p = 0.084$). Although in Cis-TACE group, PFS times were comparable between the patients of primary and non-primary treatment ($p = 0.372$), in Epi-TACE group, PFS times were significantly poorer for the patients of non-primary treatment than for the patients of primary treatment ($p = 0.017$).

Conclusions: Although there were no significant differences in the outcomes between the two groups, the effectiveness of Cis-TACE for non-primary treatment was suggested.

P1-42

Resection Versus Transarterial Chemoembolization for Patients with Advanced (BCLC Stage C) Hepatocellular Carcinoma: A Propensity Analysis

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Background: Sorafenib is the only recommended treatment for patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC). We aimed to compare surgical resection (SR) and transarterial chemoembolization (TACE) for advanced (BCLC stage C) HCC patients.

Methods: A total of 264 and 389 advanced HCC patients received SR and TACE, respectively. Among them, 163 matched pairs of patients were identified from each treatment arm by propensity score matching analysis to compare long-term survival.

Results: Of all patients, the SR group had better liver functional reserve than the TACE group. In the matched propensity model, the baseline characteristics were similar between patients receiving SR and TACE. SR provided significantly better long-term survival than TACE in all patients and in patients selected in the propensity model (both $P < 0.001$). In the Cox proportional hazards model, patients receiving TACE had a 2.393-fold increased risk of mortality compared with patients receiving SR (95% confidence interval: 1.610–3.556, $P < 0.001$).

Conclusions: SR provides significantly better long-term survival than TACE in patients with BCLC stage C HCC, and should be an integral part in the management of advanced HCC. Multidisciplinary approaches for these patients and further amendment to the BCLC classification scheme are required.

P1-43

Combined Transarterial Chemoembolization and Radiotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: An External Validation Study of Clinical Significance

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Purpose: The purpose of this study is to evaluate the relationship between portal vein tumor thrombosis (PVTT) response and clinical outcomes in the hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE) followed by radiotherapy (RT).

Methods and Materials: The 329 of the training and 179 patients of the validation set treated with TACE followed by RT (TACE-RT) from August 2002 to September 2008 who satisfied the inclusion criteria were enrolled in the present study. The median follow-up period was 11.7 months (range, 1.6 to 108.6) in the training and 11.9 months (range, 1.7 to 105.1) in the validation set.

Results: After TACE-RT, PVTT response was noticed as complete in 32 (8.0%), partial in 134 (44.7%) in the training and 24 (9.1%), 122 (46.4%) in the validation, respectively. The objective response of PVTT was significantly related with post-treatment Child-Pugh score elevation ($P = 0.001$) and Child-Pugh class ($P < 0.001$). The progression-free survival was significantly related with PVTT response ($P < 0.001$, hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.25–0.42) in multivariate analysis with nodular morphology ($P = 0.04$, HR 0.71, 95% CI 0.52–0.98), single viable ($P = 0.03$, HR 0.75, 95% CI 0.58–0.97), and 400 ng/ml or less of pretreatment α -fetoprotein ($P = 0.03$, HR 0.77, 95% CI 0.61–0.98). In the receiver-operating characteristics analysis of 1-year progression prediction, PVTT response showed area 0.74 of under curve value. Most of the findings were successfully reproduced in the independent external validation set.

Conclusions: Positive PVTT response was closely related with favourable clinical outcomes. The TACE-RT to PVTT makes it possible to maintain normal liver function, reduce metastasis and achieve longer term survival.

P1-44

Follow-Up of Patients with Massive Tumor Necrosis After Transarterial Chemoembolization

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Purpose: The purpose of this study was to evaluate clinical and radiologic findings in patients with massive tumor necrosis after transarterial chemoembolization (TACE).

Materials and Methods: We retrospectively reviewed clinical findings and radiologic findings of 10 patients who had large hepatocellular carcinoma (HCC) with massive tumor necrosis after TACE. The patients consisted of 9 males and 1 female ranging in age from 50–74 years. We performed TACE with Adriamycin and embolic materials such as polyvinyl alcohol (PVA) and gelfoam. Liver dynamic CT scans were performed before and after TACE. We evaluated clinical symptoms, laboratory findings, radiologic findings, and amount of Adriamycin and embolic materials.

Results: Mean maximum diameter of HCC on axial CT image was 10.3 cm (range: 7–18 cm). Amounts of Adriamycin were 50 mg in 8 patients and 40 mg in 2 patients. Embolic materials were PVA in 2 patients, gelfoam in 6 patients, and PVA with gelfoam in 2 patients. Mean elevated ALT after TACE was 529 IU/L (range: 104–1226 IU/L). Mean elevated AST after TACE was 694 IU/L (range: 138–1754 IU/L). Mean elevated total bilirubin was 2.3 mg/dl (range: 0.6–7.5 mg/dl). Pleural effusion was noted in 4 patients after TACE. Newly developed ascites was noted in 4 patients. Pain of patients after TACE was subsided after mean 3.8 days (range: 2–8 days). However pain was not subsided in 3 patients.

Conclusion: These clinical findings and radiologic findings were helpful for better understanding massive necrosis of HCC after TACE.

P1-45

Emergent Transarterial Embolization for Spontaneous Rupture of Hepatocellular Carcinoma: Single-Center Experience

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Objective: Liver cancer is a frequently diagnosed cancer worldwide (the fifth in men and the seventh in women). More than half a million hepatocellular carcinoma (HCC) cases are diagnosed worldwide every year. Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death in Taiwan. Spontaneous rupture of hepatocellular carcinoma is a life-threatening complication with varied incidence and high mortality. The aim of this study was to assess the clinical features and survival rate in patients with a spontaneous ruptured hepatocellular carcinoma and treated with transarterial embolization.

Materials and Methods: A 5-year retrospective study was performed on all 50 patients with spontaneous rupture of hepatocellular carcinoma and emergent transarterial embolization who presented from 2010 to 2014. The clinical features, laboratory and image findings of groups with different survival periods were compared.

Results: The group who died (n = 20) presented worse clinical condition and elder status than the group who survived (n = 30). The group who died had a poorer Child-Pugh class, lower hemoglobin and serum albumin levels, higher demand for blood transfusion, greater prevalence of portal vein throm-



Fig. 1. (for Abstract P1-45).

bosis, and higher serum total bilirubin and aspartate aminotransferase levels. Successful hemostasis with transcatheter arterial embolization was achieved in 87% of patients (30-day mortality rate, 45%). Two of the group who survived received second-stage hepatic resection.

Conclusion: Emergency transcatheter arterial embolization is a minimally invasive and effective treatment for hemostasis of ruptured hepatocellular carcinoma. However, patients with poorer clinical condition and elder status are at high risk of death.

P1-46

Partial Splenic Embolization with Transcatheter Arterial Chemoembolization in Patients with Hepatocellular Carcinoma Accompanied by Thrombocytopenia: Effect and Safety Compared to Control Group

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Background/Aims: Partial splenic embolization (PSE) has been introduced for the treatment of thrombocytopenia caused by secondary hypersplenism in patients with liver cirrhosis. We retrospectively evaluated the effects and safety of PSE with transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) accompanied by thrombocytopenia.

Methods: Eighteen HCC with cirrhotic patients were treated with TACE and PSE due to severe thrombocytopenia (platelet count $<45 \times 10^3/\text{mm}^3$). Twenty four HCC with cirrhotic patients were treated with TACE without PSE as control group. Serial transverse images of the enhanced abdominal CT scan were obtained. The splenic volume was calculated by multiplying height in PSE group. The laboratory data was examined to evaluate the therapeutic effects and the complications.

Results: The mean infarction ratio was $74.94 \pm 10.8\%$ in PSE group. The splenic volume was decreased from 688.9 ± 275.8 ml to 461.3 ± 276.1 ml after PSE ($p < 0.001$). The platelet value after PSE was significantly increased at 12 months ($p = 0.001$). The causes of HCC with cirrhosis were similar in both groups ($p = 0.326$). The CTP and MELD score were similar between groups after PSE. There were two cases of death within six month after PSE, one's condition became worse after TACE for multiple HCC and the other suffered sepsis by unknown origin.

Conclusions: PSE with TACE proved to be effective measures with less complications for treating thrombocytopenia in patient with hypersplenism and HCC. Liver function

and Child-Pugh score after PSE was similar with non-PSE patients at 1 year, concurrent PSE with TACE for HCC can maintain hepatic functional reserve. PSE may be initially recommended to patients of HCC with thrombocytopenia before TACE.

P1-47

Effects for Not Hypervascular HCC by B-TACE (Balloon-TACE)

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Background: Recently in Japan, B-TACE (Balloon-TACE) is gradually accepted for HCC treatment. But It is unknown yet what kind of case is effective. Besides TACE is not effective for not hypervascular HCC. So we examined the effect of B-TACE, especially whether B-TACE was effective for not hypovascular HCC.

Methods: From April 2013 to July 2014, we treated 72 cases, 125 nodules by B-TACE. In those patients, 41 cases, 42 nodules was treated by C-TACE (conventional TACE) previously. First we examined the differences of B-TACE effect between hypervascular HCC and not hypervascular HCC retrospectively. Secondly we divided hypervascular group and not hypervascular group. And in each groups, we examined differences of B-TACE effects and C-TACE effects. They were 72.6 years old (average), men/women 58/14, Child-PughA/B/C 52/20/0, HCV/HBV/Al/NBNC 39/3 (overlapping+)/16/17. We defined CT grade as 1 week effect by lipiodol depositing rate from 1 to 4. Besides we used treatment effect (TE, Genpatusei kangan toriatukai kiyaku) as 1 month effect. We used miriplatin with lipiodol and 1 mm gelpart.

Results: In B-TACE, hypervascular nodule was 68, not hypervascular nodule was 57. In C-TACE, hypervascular nodule was 26, not hypervascular nodule was 16. In B-TACE, CT grade was 3.60 ± 0.76 in hypervascular group, 3.12 ± 0.91 ($P = 0.0016$) in not hypervascular group. So not hypervascular group was inferior than hypervascular group. But TE was 2.96 ± 1.02 in hypervascular group, 2.78 ± 0.78 ($P = 0.36$) in not hypervascular group, plugging no differences between hyper and not hyper group. Next we examined differences between B-TACE and C-TACE. In hypervascular group, CT grade was 3.60 ± 0.76 in B-TACE, 3.46 ± 0.58 ($P = 0.39$) in C-TACE, and TE was 2.96 ± 1.02 in B-TACE, 2.73 ± 1.04 ($P = 0.36$) in C-TACE. But in not hypervascular group, CT grade was 3.12 ± 0.91 in B-TACE, 2.31 ± 1.30 ($P = 0.0057$) in C-TACE. TE was 2.78 ± 0.88 in B-TACE, 2.06 ± 1.00 ($P = 0.007$) in C-TACE. Thus for not hypervascular HCC, B-TACE is superior to C-TACE.

Conclusion: B-TACE can be one of the useful modality for not hypervascular HCC.

P1-48

Hemodynamic Changes Under Balloon Occlusion of the Peripheral Hepatic Artery

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Background: Trans-arterial chemoembolization under balloon occlusion of the feeding artery is sometimes very effective and lipiodol emulsion seems to flow into the tumor selectively.

Aims: To clarify the mechanism of selective accumulation of lipiodol emulsion from the viewpoint of perfusion change of the tumor and adjacent liver parenchyma.

Objective and Methods: Thirteen hypervascular liver tumors were analyzed. Two catheters were used: one for occlusion of the peripheral feeding artery and the other for injection of contrast material from common hepatic artery or superior mesenteric artery. CT during arteriography was performed with or without inflation of the balloon.

Results: Tumor enhancement was decreased in all cases and almost vanished in 5 under the condition of balloon inflation. In the occluded adjacent liver, parenchymal enhancement was decreased but several arterial vessels were visualized in all cases but one. Time-density curve of single level dynamic CT during arterial portography (CTAP) with or without occlusion in 7 cases revealed increased portal-venous perfusion in the occluded area in one case and no changes in the rest. In all three cases with arterio-portal shunting, defective shunting area in CTAP became faint or vanished in CTAP under balloon occlusion. Defective area of the tumor in CTAP became small in diameter under balloon occlusion compared with under no occlusion in all cases.

Discussion: Balloon occlusion of the feeding artery seems to cause complementary increase of arterial inflow of the adjacent parenchyma in the occluded area via communicating neighboring arteries. And if this mechanism did not work sufficiently, portal-venous perfusion would increase in compensation for original blood supply of the tumors. Our results also supported that in cases with arterio-portal shunting excessive injection to the shunting area would be voided under balloon occlusion.

Conclusion: Selective accumulation effect of lipiodol emulsion under balloon-occlusion may be due to complementary filling of either arterial or portal-venous perfusion.

P1-49

Usefulness of Radioembolization in Identifying Patients with Favorable Tumor Biology of Hepatocellular Carcinoma Before Living Donor Transplantation

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Purpose: Defining tumor biology before liver transplantation for HCC is of tremendous clinical significance and is critical to ensure optimal treatment outcome. In our experience of living donor liver transplantations (LDLT), we found a potential benefit of radioembolization in identifying patients with advanced HCC who have favorable tumor biology.

Materials and Methods: Initially, five patients underwent radioembolization with Yttrium-90 (⁹⁰Y)(SIR-Spheres; Sirtex Medical Ltd., Sydney, Australia) with the intention of both palliative treatment and tumor biology evaluation for potential LDLT. All patients were beyond the Milan criteria and the University of California San Francisco (UCSF) criteria on initial imaging.

Results: The target lesions of all five patients showed partial response according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) on follow-up imaging. And only 4 patients subsequently underwent LDLT using a right lobe graft. The time interval from radioembolization to LDLT was 13, 20, 32, and 40 weeks respectively. All patients are currently alive without recurrence at 16, 34, 37, and 38 months after surgery. The remaining one patient showed a rebound increase in AFP levels 7 weeks after radioembolization. Further evaluation revealed the development of portal vein tumor thrombus, and the patient was deemed inoperable.

Conclusion: Radioembolization using ⁹⁰Y microspheres showed promising results in selecting patients with advanced HCC who have favorable tumor biology.

P1-50

Prognostic Effect of Arteriportal Shunt in Radioembolization Using Yttrium-90 Resin Microspheres for Hepatocellular Carcinoma with Portal Vein Thrombosis – A Single Center Study

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Background: The aim of this study was to analyze a prognostic effect of the arteriportal (AP) shunt in Yttrium-90 (Y90) radioembolization for hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT).

Methods: A total of 20 patients with HCC and PVT were treated with Y90 radioembolization between 12/2008 and 04/2014. Each target lesions were divided in two groups which tumors with or without AP shunts. The HCCs in same areas of the AP shunt were considered as same lesion, and the HCCs without AP shunt in same patient were considered as same lesion. Radiological tumor response of the target lesions was assessed using modified Response Evaluation Criteria in Solid Tumors (mRECIST). Uni/multivariate analyses were performed.

Results: Eleven target lesions were with AP shunts and 14 target lesions were without AP shunt. Target lesions with AP shunts show 6 (54.5%) partial response (PR), 2 (18.2%) stable disease (SD) and 3 (27.3%) progressive disease (PD). Target lesions without AP shunt show 1 (7.1%) complete response (CR), 7 (50.0%) PR, 3 (21.4%) SD and 3 (21.4%) PD.

Disease control rates (CR+PR+SD) of target lesions with or without AP shunts were 72.7% and 78.6%, each ($p = 0.420$).

Conclusion: The presence or absence of the AP shunts in the target lesions was not a significant prognostic factor in patients with HCC and PVT. But prospective study with more number of the patients is possible, the result could be changed.

P1-51

The Effectiveness of ART Score in Selecting Patients for Transarterial Chemoembolization Retreatment: A Cohort Study in TaiwanChi-Lung Tseng^{1,5}, Yee Chao^{4,5}, Wei-Jen Lai², Chun-Jui Huang^{3,5}, Yi-Hsiang Huang^{1,5}, Hsiou-Shan Tseng^{2,5}, Chung-Pin Li^{1,5}, Rheun-Chuan Lee^{2,5}, Han-Chieh Lin^{1,5}

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Background: The ART (Assessment for Retreatment with Transarterial chemoembolization, TACE) score was recently developed to determine patients who may benefit from multiple sessions of TACE for treatment of hepatocel-

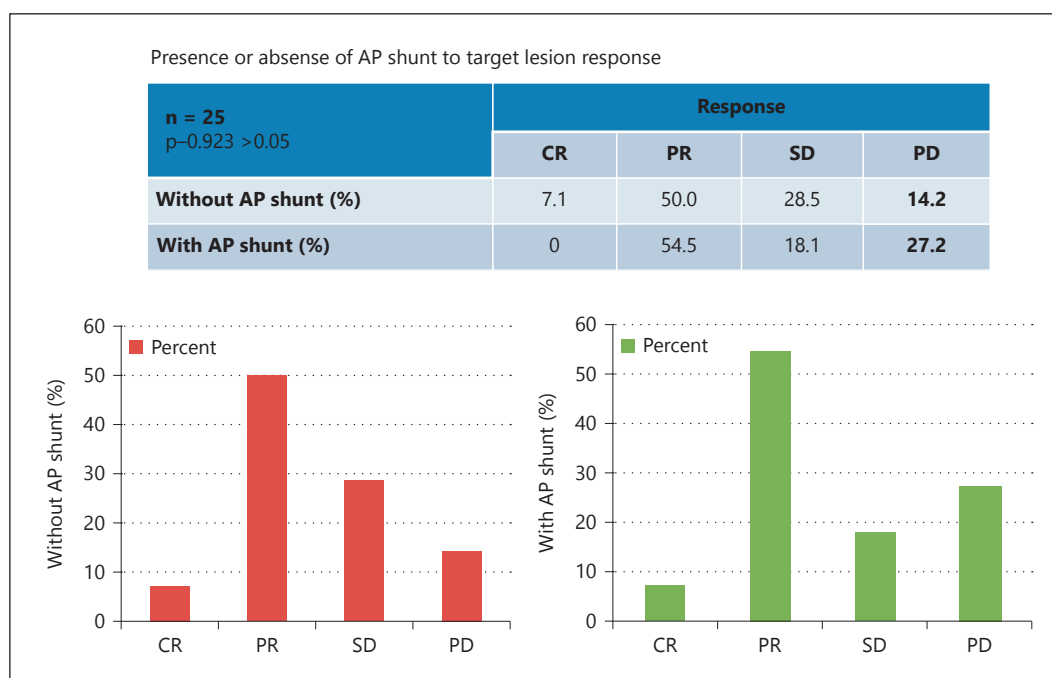


Fig. 1. (for Abstract P1-50).

lular carcinoma (HCC). The primary aim of the study was to test the validity of the ART score in a Taiwanese cohort. The secondary aims were to evaluate overall survival (OS) and clinical determinants of improved survival in patients treated with multiple TACE sessions.

Methods: The ART score, clinical characteristics and outcomes of patients with HCC who received multiple TACE sessions in Taipei Veterans General Hospital from September 2007 to July 2013 were recorded and analyzed.

Results: Among the 82 patients, 57 of them had an ART score of 0–1.5 and 25 had a score ≥ 2.5 . The median OS was 23.1 months and the overall mortality rate was 62%. The ART score was not found to be associated with survival ($p = 0.584$). Multivariate Cox regression analysis revealed that baseline characteristics including tumor size more than 7.2 cm ($HR = 4.44$, $p < 0.001$), AST not less than 95 ($HR = 2.18$, $p = 0.023$), AST increased more than 25% ($HR = 2.13$, $p = 0.019$), post/pre-TACE AFP ratio ($HR = 1.40$, $p = 0.001$), and no radiological response to TACE ($HR = 2.21$, $p = 0.021$) were independent significant predictors of survival.

Conclusions: The ART score was not found to be effective in selecting patients for TACE retreatment in our Taiwanese cohort. Large tumor size, high AST level, post/pre-TACE AFP ratio, AST increase $>25\%$ and no radiological response to TACE were independently associated with shorter survival after TACE therapy.

patients for TACE retreatment, the ABCR (Alpha-feto Protein, BCLC, Child-Pugh and Response) score was recently developed. This study was conducted to test the ABCR score in a Taiwanese cohort and to determine the clinical factors associated with survival.

Methods: The ABCR score, clinical characteristics and outcomes of patients with HCC who received multiple TACE sessions in Taipei Veterans General Hospital from 2006 to 2014 were recorded and analyzed.

Results: Among the enrolled 130 patients, the ABCR score was found to be associated with survival ($P = 0.004$). It showed a linear decrease in median overall survival when ABCR scores increased. Multivariate Cox regression analysis revealed that clinical factors including tumor size more than 7.5 cm ($HR = 2.15$, $P = 0.002$), AFP not less than 200 ng/ml ($HR = 1.77$, $P = 0.021$), AST increased more than 25% ($HR = 1.64$, $P = 0.041$), and no radiological response to TACE ($HR = 2.92$, $P \leq 0.001$) were independent significant predictors of poor survival.

Conclusions: The ABCR score was found to be effective in selecting patients for TACE retreatment in our Taiwanese cohort. Large tumor size, high level of AFP, AST increase $>25\%$ and no radiological response to TACE were associated with shorter survival after TACE therapy.

P1-52

Withdrawn

P1-53

The Effectiveness of ABCR Score in Selecting Patients for Transarterial Chemoembolization Retreatment: A Cohort Study in Taiwan

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Background: The number of optimal sessions of TACE patients with hepatocellular carcinoma (HCC) may benefit from is controversial. To aid in the clinical decision of selecting

P1-54

Prediction of Clinical Outcome After Radioembolization in HCC Patients: Role of ¹⁸F-FDG PET-CT

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Background: To investigate the prognostic value of ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) in predicting progression-free survival (PFS) after Yttrium-90 radioembolization (Y-90 RE) in patients with hepatocellular carcinoma (HCC).

Methods: Between 2009 and 2013, a total of 40 patients with HCC were treated with Y-90 RE. ¹⁸F-FDG PET-CT was performed before treatment and maximum standardized uptake value (SUVmax) was obtained in each patient. Tumor response was evaluated in accordance with modified RECIST criteria every 3 months after Y-90 RE. Chi square tests, Kaplan-Meier method and Cox proportional hazards model were used for statistical analysis.

Results: The median age was 56.5 years, and 29 (72.5%) were males; 36 (90.0%) patients were in Child-Pugh class A. Patients with low SUVmax (<6.1) had a higher disease control rate than those with high SUVmax (≥ 6.1) (55.6% vs. 23.1%, respectively; $P = 0.05$). Median PFS was significantly longer in patients with low SUVmax than those with high SUVmax (22.1 vs. 6.5 months, respectively; $P = 0.03$). In addition, a longer PFS was observed in patients with BCLC stage A or B than those with BCLC stage C ($P = 0.01$). In multivariate analyses, low SUVmax was found to be a significant prognostic factor for a lower risk of disease progression (adjusted hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.17–0.95; $P = 0.04$), along with BCLC stage A or B (adjusted HR 0.27, 95% CI 0.10–0.76; $P = 0.01$).

Conclusions: A high SUVmax based on ^{18}F -FDG PET-CT performed before treatment and BCLC stage were independent prognostic factors for PFS after Y-90 RE in HCC patients.

P1-55

The Role of ^{18}F -Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) for Accurate Staging and Optimal Treatment Planning in Patients with Hepatocellular Carcinoma

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Background and Aims: ^{18}F -fluorodeoxyglucose (FDG)-positron emission tomography (PET) is known to help detect primary hepatocellular carcinoma (HCC) and extrahepatic metastases (EHM) in patients with advanced stage. However, it surely is not cost-effective to do FDG-PET for all patients with HCC. We investigated who would benefit from FDG-PET and which factors were associated with increased FDG uptake.

Methods: 223 consecutive HCC patients who underwent PET prior to treatment between December 2005 and November 2009 were enrolled in this analysis retrospectively. Baseline characteristics as follows; median age (IQR); 57 (49–66) years, male:female; 191:32, common etiology; chronic hepatitis B of 171 (76.7%), Barcelona Clinic Liver Cancer (BCLC) stage 0 of 7, Stage A of 58, Stage B of 58, Stage C of 91, Stage D of 9.

Results: Initially recommended treatment modality was changed in 74 (33.2%) patients. They were mostly supposed to have curative treatment, but finally received IA-chemotherapy or sorafenib due to the findings of FDG-PET. In the multiple logistic regression analysis, FDG-avid HCC detected in 123 patients (55.2%) were significantly associated with male, higher level of PIVKA-II (>150 mAU/ml), and beyond Milan criteria. EHM found in 60 patients (26.9%) were also

closely related with higher level of AFP (>200 ng/ml) and DCP level (>150 mAU/ml). Beyond Milan criteria, higher MELD score, and higher FDG uptake (SUVmax) of HCC were significant risk factor for the survival after PET.

Conclusion: PET should be considered for the evaluation of HCC patients with elevated serum α -fetoprotein or DCP level and beyond Milan criteria. Thus, in such patients, optimal PET-scan complements conventional imaging for accurate staging and treatment strategy.

P1-56

The Effect of Tumor Size on the Outcome of Inoperable Hepatocellular Carcinoma After Stereotactic Body Radiation Therapy

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Purpose: Stereotactic body radiation therapy (SBRT) for inoperable hepatocellular carcinoma (HCC) offer excellent local control rates. In this study we retrospectively analyzed the influence of different tumor size on treatment outcomes after SBRT.

Methods and Materials: Between December 2008 and Feb. 2014, 141 HCC patients were treated with Cyberknife SBRT. Patient included are unresectable, unfeasible, difficult or refusal to undergo surgery or other standard therapies such as percutaneous ablative therapies or transarterial embolization; Child A or Child B score ≤ 7 , ECOG ≤ 2 , available normal liver volume at least 700 cc. The prescribed dose depended on tumor size, location and liver function; 39 Gy/3 fractions for small tumor (≤ 4 cm), 40–45 Gy for intermediate (≥ 4 –9 cm) and large (≥ 10 cm) tumors size as well as centrally located tumors. Treatment outcome, prognosis and safety were analyzed.

Results: Median follow-up was 19.5 months (range 2–72 months). A total of 52 patients with small tumors, 55 intermediate tumors and 34 large tumors patients were retrospectively analyzed. The 3-yr local control rate was 97.85%, 71.99% and 82.14% for small, intermediate and large tumor, respectively. ($p = 0.0035$). However, there were no significant differences in Overall survival rate ($p = 0.3757$), Intra-hepatic recurrence free survival ($p = 0.1577$), Disease-progression free survival ($p = 0.1874$), Distant metastasis-free survival ($p = 0.9443$). Acute toxicities $\geq$ grade 3 was observed in 3 (2.12%) patients. All but one patients promptly recovered. Grade 5 liver failure occurred in 1 patients in the intermediate tumor size group.

Conclusion: Cyberknife SBRT provides effective local control even for large solitary HCC (≥ 10 cm). With small HCC (≤ 4 cm) offer the best local control rate and response rate. In contrast, tumor size does not significantly affect the overall

survival rate, intra-hepatic recurrence free rate, disease-progression free rate and distant-metastasis free rate. Disease progression outside the targeted HCC remains a major problem, providing rationale for combining SBRT with regional and systemic therapies.

P1-57

Stereotactic Body Radiation Therapy Using Respiratory-Gated Volumetric-Modulated Arc Therapy Technique for Small Hepatocellular Carcinoma

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Background: Stereotactic body radiation therapy (SBRT) has emerged as an alternative, non-invasive local treatment option for patients with hepatocellular carcinoma (HCC) when established curative treatment modalities cannot be applied. Volumetric-modulated arc therapy (VMAT) is one of the most sophisticated linear accelerator-based treatment modalities and allows dose rate-changing intensity modulation with gantry rotation. In our present study, we report our clinical experiences with SBRT using respiratory-gated VMAT technique as an alternative treatment for small HCC.

Methods and Materials: A total of 119 patients (139 lesions) with HCC who were treated with SBRT using respiratory-gated VMAT technique were registered between March 2012 and July 2013 at our institution. A dose of 10–15 Gy per fraction was given over 3–4 consecutive days, resulting in a total dose of 30–60 Gy. Local failure was defined as the recurrence of the treated lesion; intrahepatic recurrence was defined as recurrence within the liver outside the treated lesion. Overall and recurrence-free survivals were estimated from the date of the start of SBRT to the date of death, the last follow-up examination, or to the date of tumor recurrence, respectively.

Results: The median follow-up period of all patients was 25.8 months (range, 3.2–36.8 months). The study population was mostly male (81.5%), demonstrating a median age of 60 years. One-hundred and eight (90.8%) patients had liver function of Child-Pugh class A, and median size of tumors was 1.7 cm (range, 0.8–5.8 cm). Only 3 patients were treatment-

naïve, and all other patients had received various courses (range, 1–25 courses) of previous therapies, including hepatic resection, trans-arterial chemoembolization, radiofrequency ablation, or percutaneous ethanol injection before receiving SBRT. Overall survival rates at 1 and 3 years were 99.2% and 83.8%, respectively. Local control rate at 3 years was 97.0% in all treated lesions. Intrahepatic recurrence was the main cause of failure and intrahepatic recurrence-free survival rates at 1 and 3 years were 61.5% and 33.3%, respectively. Multivariate analysis revealed that the Child-Pugh class before SBRT had significant effects on overall survival (Child-Pugh A: Hazard ratio = 0.463; 95 CI, 0.262–0.817; p = 0.008). Number of the prior treatment sessions was a statistically significant factor for intrahepatic recurrence by logistic regression analysis (p < 0.001), i.e. intrahepatic recurrence risks rise by up to 1.397 with every one of prior treatment sessions added.

Conclusions: SBRT using respiratory-gated VMAT technique was an excellent ablative treatment modality for patients with small HCC. SBRT can be a good alternative treatment for patients with small HCCs that are unsuitable for surgical resection or local ablative therapy.

P1-58

Repeated Stereotactic Body Radiotherapy for Recurrent Hepatocellular Carcinoma

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Background: Intrahepatic recurrence is the most common pattern of failure after curative treatment in the patients with hepatocellular carcinoma (HCC). In regard to primary HCC, the treatment strategy for recurrent intrahepatic HCC is determined by the function of the liver and the macroscopic tumor features. The purpose of this study is to determine the feasibility and efficacy of repeated stereotactic body radiotherapy (SBRT) for inoperable recurrent HCC.

Methods: We retrospectively reviewed 28 recurrent HCC patients who were treated with the repeated SBRT at Korea Cancer Center Hospital between January 2004 and May 2014. All patients were unsuitable for surgery or local ablation and had incomplete response to transarterial chemoembolization. Twenty-seven patients (96%) underwent the repeated SBRT for intrahepatic recurrence other than the lesion with the 1st SBRT, and only one patient underwent

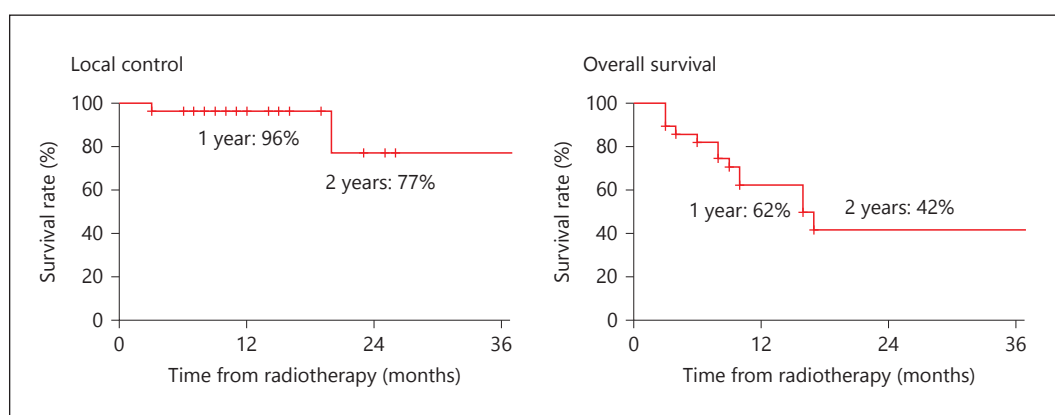


Fig. 1. (for Abstract P1-58).

re-irradiation for the same lesion with the 1st SBRT. Twenty-seven patients (96%) had Child-Turcotte-Pugh (CTP) class A (A5 in 23 and A6 in 4, respectively). The median dose was 51 Gy (range, 30–60 Gy in 3–5 fractions) and 44 Gy (range, 30–60 Gy in 3–4 fractions) in the 1st and the repeated SBRT, respectively.

Results: The median follow-up duration was 11 months (range, 2–56 months). The median interval between the first and the repeated SBRT was 11 months (range, 2–48 months). The 2-year local failure-free and overall survival rates were 77% and 42%, respectively. Three patients (11%) experienced deteriorating of CTP score by greater than or equal to 2 within 3 months of SBRT without disease progression. The total mean normal liver dose was the most significant predictor for hepatic deterioration after the repeated SBRT.

Conclusions: This study showed that the repeated SBRT can be safely and effectively administered to the patients with inoperable recurrent HCC, and these results suggest that this technique might be considered a salvage treatment. We suggest that patients with the repeated SBRT should be treated using the total mean normal liver dose constraint of 32 Gy3 or less. A further well-controlled large-scale study and longer follow-up are needed to determine the optimal dose-volume constraints and characterize late complications.

P1-59

Practical Patterns for Stereotactic Ablative Radiotherapy to Hepatocellular Carcinoma in Korea: A Survey of the Korean Stereotactic Radiosurgery Group

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Purpose: To investigate practical patterns for stereotactic ablative radiotherapy (SABR) to hepatocellular carcinoma (HCC) in Korea.

Methods and Materials: The Korean Stereotactic Radio-surgery Group of the Korean Society for Radiation Oncology (KROG 13-14) conducted a national patterns-of-care survey about liver SABR in HCC, consisting of 18-questions and 2 clinical scenarios in June 2013.

Results: All 208 radiation oncologists (100%) in Korea responded to this survey. Among these, 95 radiation oncologists were specialists for hepatology: 64 physicians did not use SABR for HCC; 31 physicians used SABR. Most physicians (52%) conducted SABR to HCC in ≤5 cases per year. There was a variety of prescribed doses according to tumor size and baseline Child-Pugh (CP) class. For 2.8 cm HCC with CP class of A, all physicians selected SABR and the preferred dose was 60 Gy in 3 fractions. For CP class of B, 23 physicians (74%) selected SABR and the preferred dose was 60 Gy in 3 fractions. For 5 cm HCC with CP class of A, 19 physicians (61%) selected SABR and the preferred dose was 60 Gy in 3 fractions. For CP class of B, 14 physicians (45%) selected SABR and the preferred dose was 60 Gy in 3 or 4 fractions.

Conclusions: There was a diversity of liver SABR practices for HCC among radiation oncologists in Korea. These findings underscore the need for additional prospective studies to standardize the practice of SABR.

P1-60

Combination Treatment of Trans-arterial Chemoembolization Followed by Radiotherapy with Hyperthermia (CERT) in Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: Interim Analysis of Prospective Phase II Trial

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Purpose: The purpose of the present study is to evaluate the objective response and toxicity of the trans-catheter arterial ChemoEmbolization (TACE) followed by Radiotherapy (RT) and hyperThermia (CERT) in hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT).

Methods: This study is designed as a single-center, non-randomized prospective phase II trial subjective of HCC with PVTT. The patient was first treated with TACE, and after one week the four-dimensional computed tomography simulation

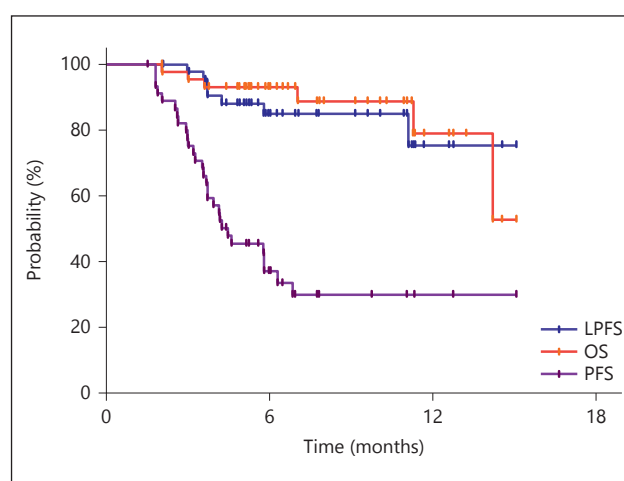


Fig. 1. (for Abstract P1-60).

and first session of hyperthermia were conducted. The respiration gated RT planned as ten fractions started after another one week. Six sessions of hyperthermia according to the energy escalation protocol was delivered twice a week. Response evaluation was planned at one month after RT completion using modified response evaluation criteria in solid tumors, and toxicity was checked by using the Common Terminology Criteria for Adverse Events Version 4.0.

Results: This interim analysis was conducted with the patients enrolled from October 2013 to November 2014. During the study period, 56 patients were screened and 51 of them consented to participate in this trial. And finally 46 patients (90.2%) who received at least one session of hyperthermia were eligible and enrolled. Six sessions of hyperthermia were completed in 33 patients (64.7%). The median follow-up was 6.7 months (range, 2.0 to 15.0 months). Overall, complete response was observed in 10 (21.7%), partial response in 27 (47.8%), and stable disease in 5 (10.9%) patients. Most of the toxicities were grade I or II. There was one death related with severe pneumonia of unknown cause in contralateral lung which was developed one month after treatment. And one patient could not complete planned treatment because of continuous elevation of bilirubin after TACE. As a late toxicity, no classic radiation induced liver disease was developed and 13 (28.3%) asymptomatic gastro-duodenal toxicities were noticed in routine esophagogastro-duodenoscopy. The local progression-free survival, progression-free survival, and overall survival rates were 75.1%, 29.8%, and 78.9% at one year, respectively, as displayed in figure 1.

Conclusions: Despite the sample size and follow-up period are not enough to draw concrete conclusion at present, CERT showed promising response rate with acceptable toxicities in HCC patients with PVTT. Acknowledgements: This research was supported by a Samsung Medical Center grant (GF01130081).

P1-61

Efficacy of Radiation Therapy for Macroscopic Vascular Invasion of Advanced Hepatocellular Carcinoma

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Purpose: Radiotherapy (RT) technology has been significantly developed in last two decades and RT for hepatocellular carcinoma (HCC) is rapidly increasing. Macroscopic vascular invasion (MVI) is an critical prognostic factor in advanced HCC, and improvement of MVI is considered to improve survival. In our institution, RT combined with hepatic arterial infusion chemotherapy (HAIC) or trans-arterial chemoembolization (TACE) to treat MVI in advanced HCC was increasing. The aim of this study was to investigate the survival and therapeutic effect after RT for MVI in advanced HCC, and to evaluate the clinical factors influencing on survival and therapeutic effect.

Method: We retrospective investigated 47 HCC with MVI treated with RT from April 2008 to March 2014. Median survival time (MST), was estimated by Kaplan-Meier method. Therapeutic effect of irradiated area was evaluated according to RECIST. Clinical factors influencing on MST and therapeutic effect were identified using univariate and multivariate analysis.

Results: 23 had MVI with hepatic vein or inferior vena cava tumor thrombus (VV), 24 with portal vein tumor thrombus (VP). Child Pugh class A: B = 24: 23. Mean maximum tumor diameter was 7.8 cm, tumor number ≤ 3 : >3 = 27: 20, extrahepatic metastasis present: absent = 11: 36. 43 were combined with HAIC or TACE. The mean radiation dose was 43 Gy. MST was 12.8 Month. CR or PR rate of irradiated area was 64%. Multivariate analysis revealed that independent predictive factor of survival was CR or PR of irradiated area. (95% CI: 0.055–0.416) In CR or PR group, MST was 18.7 month whereas SD or PD group was 4.2 month. Independent predictive factor of CR or PR of irradiated area was presence of VV. (95% CI: 0.026–0.859) CR or PR rate of VV group was 87% whereas VP group was 44%. Severe adverse event (SAE) were observed in 8 cases. 4 had hepatic failure, 2 had gastroduodenal bleeding, 2 had constrictive pericarditis. 2 were Child A cases, and 6 were Child B cases. SAE were more frequently in Child B than Child A.

Conclusion: Prognostic factor after RT for HCC with MVI were good therapeutic effect of irradiated area, and therapeutic effect was better with VV than VP. SAE were lower in Child A than Child B. In conclusion, RT for MVI was a useful therapeutic option in advanced especially in VV and Child A.

P1-62

Survival Analysis of Radiotherapy with Helical Tomotherapy for Pulmonary Metastases from Hepatocellular Carcinoma

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Radiotherapy is becoming a useful local control therapy for lung cancer; however, few data have been available about palliative radiotherapy with Helical tomotherapy for pulmonary metastases (PM) from hepatocellular carcinoma (HCC). To confirm the role for this treatment on PM and investigate the prognostic factors for the patients, we retrospectively studied 41 patients with pulmonary metastases from HCC who had been treated with radiotherapy in our institution. Radiotherapy with Helical tomotherapy was designed to focus on the lung lesions with or without primary intrahepatic tumors to deliver a palliative dose ranged from 40 to 60 Gy, while the intrahepatic lesions were treated with surgery or liver transplantation or transarterial chemoembolization (TACE) before radiotherapy. Follow-up period from radiotherapy ranged from 3 to 35 months (median, 13.5). An objective response rate was (65.8%) observed in the subjects by computed tomography imaging. Analysis of patient characteristics for progression-free survival (PFS) or overall survival (OS) indicated that radiotherapy in combination with sorafenib was associated with better survival than radiotherapy only (median PFS, 12.2 vs. 5.8 months, $P = 0.008$; median OS, 17.5 vs. 15.9 months, $P = 0.036$). After multivariate adjustment, radiotherapy alone group remained significant for an increased risk of progression than radiotherapy combined sorafenib group (hazard ratio = 2.51; 95% confidence interval = 1.09–5.79; $P = 0.031$). Moreover, number of lung lesions for PFS and intrahepatic tumor for OS were also found to be significant in both univariate and multivariate adjustment (median PFS for number of lung lesions, 8.7 vs. 5.2 months, $P = 0.01$; median OS for intrahepatic tumor status, 20.1 vs. 12.3 months, $P = 0.006$). Thus, radiotherapy with Helical tomotherapy for PM-HCC in selected patients is feasible and resulted in relatively good outcomes with regard to PFS or OS.

P1-63

**Radiotherapy for Adrenal Metastasis
from Hepatocellular Carcinoma:
A Multi-Institutional Retrospective Study**

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Background: Adrenal gland is one of the common metastatic sites from hepatocellular carcinoma (HCC), however, it was unclear to know the effectiveness of radiotherapy regarding to tumor response, survival benefit, or beneficial subgroup for radiotherapy. We performed this multiinstitutional study with subjects obtained from 9 hospitals of the Korean Radiation Oncology Group (KROG) to investigate tumor response, overall survival (OS), and prognostic factors for OS after radiotherapy.

Methods: After approval by the KROG (KROG 13-05), we retrospectively reviewed 134 patients who completed a planned radiotherapy for their adrenal metastases which were diagnosed pathologically or clinically by using computed tomography, and/or magnetic resonance imaging, and/or angiograph. We excluded patients who had prior treatment to adrenal metastases. Tumor response was defined at the time of each maximal response according to the Response Evaluation Criteria in Solid Tumors criteria (version 1.1). The probability of cumulative survival was calculated using the Kaplan-Meier method. Multivariate analysis was performed with a Cox proportional hazards model. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events (version 4.2).

Results: A total of 142 adrenal metastases in 134 HCC patients were included between May 2000 and December 2012. A median age was 59 years (range: 35–76 years). Thirty (21.7%) patients were no evidence of intrahepatic HCC and 93

(67.4%) patients were no evidence of extrahepatic metastasis except adrenal metastases at the time of diagnosis of adrenal metastases. The median tumor size was 4.7 cm (range: 1.0–15.0 cm). Because there was variation in the total dose and in the fraction dose, we used the biologically effective dose (BED) for analysis, and a median BED was 58.5 Gy₁₀ (range: 25–112.5 Gy₁₀). A complete response (CR) was noted in 6 (4.3%), and a partial response (PR) in 48 (34.0%), yielding an objective response rate of 38.3%. There was no significant correlation between objective response and radiation dose (BED: $p = 0.199$). The median time from radiotherapy to maximal response for patients who achieved objective response was 3 months (range: 1–8 months). The median OS was 12.8 months, and the 1-, 2-, and 5-year OS rates were 53.1%, 23.9%, and 9.3%, respectively. According to CTCAE criteria, grade 3 anorexia occurred in 2 patients, grade 3 diarrhea in 1 patient, and grade 3 fatigue in 1 patient. Late gastrointestinal bleeding occurred in 4 patients. On univariate analysis, controlled intrahepatic tumor, no extrahepatic metastases except adrenal metastasis, controlled extrahepatic metastasis except adrenal metastases, tumor size <4.7 cm, AFP value <400 ng/ml, and Child-Pugh (CP) class A were related to favorable OS. Multivariate analyses revealed that the following factors had significant effects on OS: controlled intrahepatic tumor (hazard ratio [HR] = 0.427; 95% CI, 0.250–0.728; $p = 0.002$); controlled extrahepatic metastasis (HR = 0.568; 95% CI, 0.368–0.877; $p = 0.011$); and CP class A (HR = 0.463; 95% CI, 0.271–0.792; $p = 0.005$). Among 19 patients of good prognostic group, 84.2% achieved disease stability, which is CR, PR, or stable disease.

Conclusions: Although the patients with adrenal metastasis from HCC had poor OS, radiotherapy for adrenal metastases is a meaningful treatment modality in respect to disease stability, especially for the good prognostic group.

P1-64

**Long-Term Outcome of Proton Beam
Therapy for Treatment-Naïve Patients
with Hepatocellular Carcinoma**

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Background & Aims: We and others have reported on the excellent efficacy and safety of proton beam radiotherapy (PBT) for hepatocellular carcinoma (HCC). However, these reports were mostly for the recurrent HCC cases, and no study has demonstrated the long-term outcome of PBT for naïve HCC patients. We thus analyzed the long-term efficacy and safety of PBT for treatment-naïve HCC.

Methods: One hundred eighty four patients who received PBT for naïve HCC since 1991 were analyzed.

Results: Five-year local tumor control rate was 87%. Three-year, 5-year, and 7-year overall survival (OS) rates were 67%, 47%, and 32%, respectively, with median survival time (MST) of 58 months. Of the 184 cases, 97 cases were operable but preferred PBT rather than hepatic resection. Their 3-year, 5-year, and 7-year OS rates were 75%, 55%, and 44%, respectively, with MST of 67 months. Cox multivariate analysis revealed patient's age, Child Pugh score and ECOG performance status as significant factors affecting the long-term OS: tumor size and the presence of vascular thrombus were not significant. Neither treatment-related death nor complications of grade 3 or more were observed.

Conclusions: PBT demonstrated excellent long-term local tumor control and OS for treatment-naïve HCC cases. These results support the role of PBT as a non-invasive, safe yet curative therapeutic option for HCC. PBT is especially good for large HCC, advanced HCC with vascular invasions, and also aged patients.

P1-65

Proton Beam Therapy for Hepatocellular Carcinoma with Extensive Portal Vein Tumor Thrombosis

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Background: To evaluate the efficacy of proton beam therapy (PBT) for hepatocellular carcinoma with extensive tumor thrombosis in the main trunk or major branches of the portal vein.

Methods: Eighty patients with hepatocellular carcinoma were treated by PBT. There were 65 men and 15 women, and the median age was 65 years old (range: 25–88). The CTV ranged from 15.2 cm³ to 1687 cm³ (median: 238.9 cm³). The clinical stages were 3B, 3C, 4A, and 4B in 65, 1, 5, and 9 patients, respectively. Thirty-two patients had primary tumors, and 48 had recurrent tumors. The delivered total dose ranged from 70 to 80.47 Gy₁₀ (median: 80.47Gy₁₀) in terms of equivalent dose in 2Gy fractions.

Results: Seventy-seven patients (96.3%) completed the planned treatment. Median survival rate for all the patients was 12 months. MST for the patients treated with PTV that encompassed all the detectable lesions was 26.9 months, and MST for the patients who had viable tumor outside of their PTV was 6.3 months. Local recurrence after PBT was observed

in 3 patients. Forty-five patients died of tumor progression, and 28 of them had recurrence out of the PTV. Multivariate analysis revealed existence of viable tumor outside of the PTV, clinical stage, and value of desgamma-carboxy prothrombin as significant factors affecting the OS.

Conclusions: PBT was effective for patients with extensive portal tumor thrombus, if the PTV encompassed all the detectable lesions.

P1-66

The Effect of Radiotherapy in Liver-Confined But Non-Resectable BCLC Stage C Hepatocellular Carcinoma: Propensity-Matched Analysis Based on Nationwide Multicenter HCC Cohort

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Background: The aim of this study is to validate the efficacy of radiotherapy (RT) compared to other treatments and to identify the clinical features which showed survival benefit by RT in liver-confined but Barcelona Clinic Liver Cancer (BCLC) stage C non-resectable hepatocellular carcinoma (HCC).

Methods: HCC data from the Korea Central Cancer Registry were used to perform the systemic randomized sampling. The database, collected from 47 institutions in Korea, included information about age, gender, performance status (PS), smoking history, pack years, tumor size, α -fetoprotein (AFP), Child-pugh class or score, number of tumor mass, nodal metastasis, portal vein (PV), hepatic vein, bile duct, hepatic artery invasion, the etiology of HCC and survival. A total number of patients were 4596. Among them, we excluded patients according to the exclusion criteria as follows: 1) BCLC A, B, and D; 2) distant metastasis; 3) patients who underwent surgery as the first treatment or no treatment; 4) missing information for clinical factors. In this study, a total of 593 patients were included. Sixty-seven patients were treated with RT and defined as RT group. The others were sorted as non-RT group. Among RT group, 52 patients underwent treatments that combined RT and other treatment

within 4 weeks after the first treatment and were defined as combination RT group. The rest who received only RT was defined as RT only group. We performed propensity score matching (PSM) of 1 to 1 ratio to compare RT or combination RT group with non-RT group, respectively. PSM was also performed for subgroup with tumor size ≥ 10 cm. The endpoint was overall survival (OS). All statistical analyses were 2-sided with $P \leq 0.05$ and conducted using SAS, version 9.2.

Results: Median follow-up time for surviving patients was 48 months (range, 36.6–72.5). Before PSM, non-RT group ($n = 526$) showed significantly longer OS than RT group ($n = 67$, median survival time (MST) 12.3 vs. 8.4 months, $P = 0.001$), and there was significant difference in PS, PV invasion, age, tumor size, and AFP between two groups. After PSM between RT and non-RT groups ($n = 67$), all clinical factors were evenly distributed between two groups. In survival analysis, OS of RT group was not significantly different from that of non-RT group (Hazard ratio (HR) 1.34, 95% confidence interval (CI) 0.94–1.91, $P = 0.11$). In RT group, combination RT group improved significantly OS compared to RT only group (10.2 vs. 4.6 months, $P = 0.01$). To verify the effect of RT combining other treatment, we also performed PSM to compare combination RT group ($n = 52$) with non-RT group. After PSM, the OS of combination RT and non-RT group was not statistically different, although combination RT group had longer MST (10.7 vs. 6.9 months, HR 1.01, 95% CI 0.65–1.55, $P = 0.98$). Thereafter, we conducted PSM between combination RT and non-RT groups in subgroup with tumor size ≥ 10 cm ($n = 31$). We observed that there was significant difference of MST between two groups (10.1 vs. 5.4 months, bootstrap 95% CI of difference in MST, 0.2–11.8), and combination RT group achieved better OS despite no statistical significance (HR 0.69, 95% CI 0.4–1.19, $P = 0.17$).

Conclusions: This nationwide retrospective cohort study demonstrates that the survival outcome of RT combining other therapy was comparable to those of other treatments. Radiotherapy as a combined modality can be one of the options for this liver confined but non-resectable BCLC C HCC patients.

P1-67

Combination of Sorafenib and Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Venous Invasion

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Background: Patients with advanced hepatocellular carcinoma (aHCC) and portal vein tumor thrombus (PVTT) still have a very poor prognosis, even though the oral multi-kinase inhibitor sorafenib has revolutionized treatment of aHCC in patients with liver cirrhosis (LC). Standardization of multimodal therapy for aHCC with PVTT has not yet achieved.

Aim: This retrospective study was performed to clarify the usefulness of combined treatment with sorafenib (SF) and hepatic arterial infusion chemotherapy (HAIC) for LC patients with aHCC and PVTT.

Patients/Methods: Twenty adult Japanese patients with LC underwent HAIC (HAIC group) between 2002 and 2009, while 18 patients received HAIC after treatment with sorafenib between 2009 and 2013 (SF+HAIC group). HAIC (LV at 12 mg/hr, CDDP at 10 mg/hr, and 5-FU at 250 mg/22 hr) was performed via the proper hepatic artery every 5 days for 4 weeks using a catheter connected to a subcutaneously implanted drug delivery system.

Results: Among patients with Child-Pugh class A disease, the median survival time of the SF-HAIC group (315 days) was significantly longer than that of HAIC group (197 days), while there was no significant difference between the two groups (234 and 228 days) among patients with Child-Pugh class B disease. HAIC led to a partial response (PR) in 16.7% of patients with class A disease and 21.4% of patients with class B disease. With SF-HAIC group, PR was obtained in 63.8% and 42.9% of patients, respectively, although the PR rate was only 9.1% and 0.0%, respectively, after treatment with sorafenib alone for four weeks.

Conclusion: When multimodal therapy is employed for patients with LC in Child-Pugh class A disease with aHCC and PVTT, performing HAIC after four weeks of sorafenib treatment might improve both the tumor response and patient survival.

P1-68

Transarterial Chemoembolization with or Without Sorafenib for Intermediate-Stage HCC: Reconsidering Combination Therapy Trial Design

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Background: The proof of the superiority of combination therapy with sorafenib and transarterial chemoembolization (TACE) over TACE alone for hepatocellular carcinoma (HCC) in term of survival is lacking. The aim of this multicenter retrospective study is to evaluate the efficacy of combination therapy over TACE alone, and to compare the overall survival (OS) between the patients with $\geq$ grade 2 sorafenib-related dermatologic AEs in the combination therapy group and patients treated with TACE alone.

Methods: From January 2009 to December 2012, 606 consecutive patients with intermediate stage HCC, Eastern Cooperative Oncology Group performance status 0-1, and Child-Pugh class A-B (≤ 7) were included. Of them 202 received

combination therapy and 404 received TACE alone therapy, respectively. The patients with the appearance of $\geq$ grade 2 dermatologic AEs within the 2 months of sorafenib initiation were defined as responders to the combination therapy; whereas the patients with $\leq$ grade 1 dermatologic AEs were defined as non-responders. To reduce the impact of selection bias on the estimation of treatment effects, propensity score matching was used to adjust for the baseline differences.

Results: There was no significant difference between the two groups in median OS although a trend toward longer survival was observed in the combination therapy group (22.3 vs. 18.1 months, $P = 0.281$). After propensity score matching the difference in OS was still not different (22.3 vs. 17.9 months, $P = 0.343$). Of note, 119 non-responders in the combination therapy group had an increased risk of death compared with 83 responders (HR = 1.85; 95% CI 1.27–2.68; $P = 0.001$). To further investigate the efficacy of combination therapy, we compared the subgroup of patients who were responders in the combination group ($n = 83$) with the cohort of patients treated with TACE alone ($n = 404$). After the propensity score matching, a significantly prolonged median OS was observed in the responders subgroup (27.9 vs. 18.3 months, $P = 0.046$).

Conclusions: Combination therapy, not in all, but in responders to sorafenib, results in longer overall survival than TACE alone. Sorafenib-related dermatologic AEs may be considered a possible clinical marker to stratify responders from all patients.

P1-69

TACE Combined with Sorafenib Versus TACE Monotherapy in the Treatment for BCLC Stage B Hepatocellular Carcinoma: A Propensity Score Matched Cohort Study

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Background: This retrospective study compared the efficacy of transarterial chemoembolization (TACE)+sorafenib compared with TACE monotherapy in the treatment of BCLC stage B hepatocellular carcinoma (HCC).

Methods: Patients with BCLC stage B HCC who received TACE monotherapy ($n = 144$) or TACE+sorafenib ($n = 46$) at the First Affiliated Hospital, Sun Yat-Sen University between January 2008 and January 2014 were enrolled. Clinicopathological characteristics, response to treatment, adverse events, and survival were evaluated. Patients were matched 1:1 using the propensity score approach.

Results: Median overall survival was 18.0 months in the TACE+sorafenib group compared with 10.0 months for the TACE group ($P = 0.002$). In matched patients, multivariate analyses showed that TACE+sorafenib (HR = 0.351, 95% CI:

0.215–0.574; $P < 0.001$) and the presence of multiple-diffuse nodules (HR = 0.497, 95% CI: 0.293–0.884; $P = 0.010$) were associated with a better prognosis. In all patients, multivariate analysis revealed that only TACE+sorafenib treatment (HR = 0.602, 95% CI: 0.423–0.857; $P = 0.05$) was independently associated with a better prognosis. Although there were differences in the extent of tumor vascularity between the groups after propensity score matching (PSM), a survival benefit in patients who had hypovascular HCC treated with TACE+sorafenib was observed ($P = 0.012$ before PSM, $P = 0.001$ after PSM). Although the cumulative incidence rate of adverse events was not significantly different between the groups (all $P > 0.05$), a higher proportion of patients in the combination therapy group had hand-foot skin reaction (58.70%) and diarrhea (60.87%).

Conclusions: TACE+sorafenib combination therapy was independently associated with a better prognosis and longer survival in patients with BCLC stage B HCC. Although patients with hypovascular tumors tended to be the optimal candidates for combined therapy, further studies with larger cohorts are required to confirm this observation.

P1-70

Combined Sorafenib and TACE Treatment of Unresectable Hepatocellular Carcinoma in a Chinese Population: Subgroup Analysis of the Gideon Study

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Background: Sorafenib, a multi-kinase inhibitor, has been shown to be effective in the treatment of unresectable hepatocellular carcinoma (HCC). This study aimed to analyze the safety & efficacy of sorafenib-related therapy under real-life practice conditions.

Methods: A total of 338 Chinese patients with unresectable HCC from the international database of the GIDEON non-interventional trial were included in this analysis. All patients received sorafenib and 226 patients were treated with TACE prior to sorafenib therapy, and 80 patients were concomitantly treated with sorafenib and TACE. Endpoints were overall survival (OS), progression-free survival (PFS), time to progression (TTP) and safety.

Results: Two major patterns were observed in the use of sorafenib and TACE in current Chinese clinical practice: one is to use sorafenib posterior to TACE ($n = 226$, 66.9%); and the

other is the concomitant use ($n = 80$, 35.4%). Baseline statuses were different between both populations: BCLC-C&D patients accounted for 68.8% in those undergoing prior TACE; whereas for patients with concomitant TACE, it was 57.5%. From initial diagnosis to study entry, tumor progression can be seen despite the combination pattern of TACE and sorafenib: percentages of BCLC-C&D in patients with TACE prior to sorafenib were 58% and 68.8% at those two timepoints, respectively; similarly, for those patients with concomitant TACE, relevant data were 40.0% and 57.5%. So was the results of liver function status in patients with prior TACE treatment: Class B/C (score³ 7.0) with minor change in Child-Pugh score from 8.8% patients at initial diagnosis to 15.1% before the study entry; but such trend was not found in patients undergoing concomitant use of sorafenib and TACE (8.8 at initial diagnosis and 10.0% at study entry). For patients undergoing prior-TACE, the OS was 354 days, PFS was 168 days, and TTP was 214 days. And for those with concomitant TACE, the OS was 608 days, PFS was 201 days, and TTP was 205 days. The study observed 33.3% of patients suffering from drug-related adverse effects if the patients received sorafenib therapy after the TACE treatment, and 50.0% of patients suffering from drug-related adverse effects if the patients received concomitant treatment of sorafenib with TACE.

Conclusions: Various patterns are found in the use of sorafenib in real-world clinical practice in China. Sorafenib was usually used under the situation of tumor progression or bad liver function status after TACE treatment. Under such situation, patients who received sorafenib posterior to TACE (most popular combination model of TACE and sorafenib) still gained a relatively satisfied OS, PFS, and TTP, and acceptable adverse events. And for patients with concomitant TACE, these numbers are even higher but the different baseline statuses should be noticed.

P1-71

The Efficacy of Long-Term Treatment of Sorafenib for Advanced Hepatocellular Carcinoma

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Background: Sorafenib is the standard systemic therapy approved for treatment of advanced hepatocellular carcinoma in patients with preserved liver function and can improve the survival of such the patients. But only the small data is available on the long term administration of sorafenib.

Methods: A total of 10 patients who continue sorafenib treatment for more than 2 years were included. (3 cases continue more than 3 years) We investigate the characteristics of the long-term treatment group to explore the better way of using sorafenib for the treatment of hepatocellular carcinoma.

Results: Average age was 66. All were Males. In underlying liver disease, Five was in HCV, One was in HBV, Two were in Alcoholic liver disease and the other was in cryptogenic. The liver function of all patients were classified to Child A. Eight were in BCLC-C stage and the other 2 were in BCLC-B stage. The reasons for usage of sorafenib were; extrahepatic metastasis in 8, sequential of TACE in 2. Three patients achieved complete response. (Two patients showed disappearance of lung metastasis, one patient showed disappearance of LN and bone metastasis.) Seven of Ten patients needed salvage therapy during sorafenib treatment because of disease progression. (TACE/HAIC for intrahepatic progression in 5 patients, radiation therapy for LN in 1, TACE+RFA for LN metastasis in 1, cryoablation therapy for bone metastasis in 1, surgical resection for intrahepatic recurrence in 1) During salvage treatment, sorafenib was not stopped except for the short cessation. After the salvage therapy, sorafenib were continued as long as possible, if tolerable. In the case of reprogression of the disease, optimal treatment were added without discontinuation of sorafenib. In our study, Sorafenib were discontinued in 4 patients out of 10 (cerebral hemorrhage in 1, hemoptysis because of lung metastasis progression in 1, deterioration of liver function due to disease progression in 1, severe diarrhea in 1). Six patients are under ongoing treatment currently. Average treatment period was 34.2 months (24–68). The mean survival time from the induction of sorafenib was 35.6 months.

Conclusion: Long-time treatment of sorafenib led to good outcome in the patients with advanced hepatocellular carcinoma. The continuation of sorafenib even after the disease progression are thought to be very important for the improvement of prognosis.

P1-72

Sorafenib Therapy Following Resection Prolongs Disease-Free Survival in Patients with Advanced Hepatocellular Carcinoma at High-Risk for Recurrence

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Background: Sorafenib is the standard systemic treatment for patients with advanced hepatocellular carcinoma (HCC); however, its therapeutic value in HCC patients following resection remains controversial. This retrospective study was undertaken to assess the effects of sorafenib treatment following surgical resection in HCC patients with advanced disease and at high risk for recurrence.

Methods: Between July 2010 and July 2013, a consecutive cohort of 42 patients with advanced HCC and at high risk of recurrence (i.e., those with portal vein tumor thrombus, adjacent organ involvement or tumor rupture) who underwent resection was analyzed. The patients were categorized into the sorafenib group (n = 14) or the best supportive care (BSC) group (n = 28). Sorafenib therapy was initiated 7 days after surgery with an initial dose of 400 mg sorafenib twice daily; the dose was reduced in the event of unacceptable drug-related side effects. Differences between groups were compared using Pearson Chi-square or Fisher's exact tests for categorical data; two-sample t-tests were used for continuous data. Disease-free survival (DFS) data were represented using Kaplan-Meier survival curves by group and compared using Log-rank tests. Univariate and multivariate Cox-regression analyses were performed to identify the prognostic factors associated with DFS.

Results: Although the histological grade, BCLC stage, tumor size, nodule number, and proportion of patients with high serum alpha-fetoprotein levels were comparable between the sorafenib and BSC groups, those receiving sorafenib following resection had significantly longer DFS as compared to the BSC group (5.2 months, 95% confidence interval [95% CI]: 1.2–9.2 months and 1.8 months, 95% CI: 0.6–3.0 months, respectively). No differences in overall survival were noted between the groups. No drug-related adverse events resulted in discontinuation of the sorafenib therapy. Univariate log-rank analysis revealed that sorafenib treatment (Hazard ratio [HR]: 0.243, 95% CI: 0.098, 0.599; p =

0.002) and previous treatment before resection (HR: 0.204, 95% CI: 0.059, 0.703; $p = 0.012$) were significantly related to longer DFS; however, only sorafenib therapy was associated with longer DFS by multivariate analysis (HR: 0.363, 95% CI: 0.136, 0.966; $p = 0.042$).

Conclusions: Sorafenib was well-tolerated and improved DFS in patients with advanced HCC who underwent hepatic resection. Thus, tumor resection followed by sorafenib therapy may represent a therapeutic option for patients with advanced HCC, which will be confirmed with larger, multi-center studies.

P1-73

Long Term Follow-Up of Patients with Advanced Hepatocellular Carcinoma Who Achieved Complete Remission After Sorafenib Therapy

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Background: Sorafenib is a potent multikinase inhibitor that improves overall survival in patients with advanced hepatocellular carcinoma (HCC). Although sorafenib has efficacy in advanced HCC, response rate was varied in patient with advanced HCC. We analyzed cases of complete response after sorafenib therapy in patients with advanced HCC in Korea.

Methods: 523 patients with advanced HCC were treated with sorafenib from 3 large tertiary referral hospitals in Korea. The patients received sorafenib initially at a dose of 400 mg orally, twice daily. Tumor response and recurrence rates were assessed by radiologic study and tumor marker.

Results: Six patients with advanced HCC achieved complete response after sorafenib therapy. Median period of tumor-disappearance and observed disease-free was 4 months and 23 months, respectively. Four patients continued sorafenib after complete response. Three patients recurred after sorafenib therapy (one patient; extra- and intra-hepatic metastasis, two patients; intra-hepatic metastasis). Mortality, which was not related with disease progression or adverse effect of drug, occurred in two of six patients.

Conclusions: Although the number of cases is small, recurrence rate is relatively high. Maintenance of sorafenib therapy and subsequent treatments after sorafenib therapy should be needed to be investigated after achieving complete remission. Further studies should be needed to identify the molecular and clinical features of these tumors.

P1-74

Characteristics of the Patients with Hepatocellular Carcinoma Treated with Sorafenib Over One Year

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Background: After the efficacy and the safety of sorafenib were demonstrated in two randomized studies, sorafenib has been considered as a standard therapy for advanced hepatocellular carcinoma (HCC). Although the response rate was not high and median survival time was less than one years, some patients could be treated with sorafenib for a long time. In this study, we examined the characters of the patients treated with sorafenib over 1 year and tried to elucidate the good candidates for the sorafenib treatment.

Methods: Fifty two consecutive HCC patients treated with sorafenib over 2 weeks in our institute between July 2009 and January 2014 were enrolled in this study. We compared the clinical characteristics of the patients treated with sorafenib over 1 year ($n = 11$) and less than 1 year ($n = 41$). This study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by our institutional review board.

Results: Mean age of the patients was 66 y.o. and 46 (88%) were male. Thirteen (25.0%) and 26 (50.0%) patients were positive for HBV and HCV, respectively. Child-Pugh score was 5, 6, and 7 in 28, 19, and 5 patients, respectively. Cancer stage was 2, 3, 4a, and 4b in 3, 4, 17, and 28, respectively. The initial dose of sorafenib was 800 (400) mg in 41 (10) patients. Median treatment period was 379 days and median survival time was 850 days. The patients who could be treated with sorafenib more than one year showed low aspartate aminotransferase (37.5 vs. 56.1 IU/L, $p = 0.03$), low gamma-glutamyl transpeptidase (59.5 vs. 141 IU/L, $p = 0.01$), high serum albumin (3.9 vs. 3.6 g/dl, $p = 0.03$), and low Child-Pugh score (5.1 vs. 5.7, $p < 0.001$) before the treatment. No difference was observed between the two groups in tumor stage, starting dose, performance status, and serum levels of tumor markers such as alpha-fetoprotein and des-gamma-carboxyprothrombin. The reasons of stop medication within one year were progression of cancer ($n = 12$), deterioration of liver function ($n = 7$), worsening of performance status ($n = 3$), dermatological adverse event ($n = 3$), and renal failure ($n = 3$). Meanwhile, the reasons in patients treated with sorafenib over 1 year were worsening of performance status ($n = 3$), appetite loss ($n = 2$), infection ($n = 2$), and dermatological adverse event ($n = 1$). The rest ($n = 3$) of the patients were still taking sorafenib.

Conclusion: Liver function rather than tumor stage before starting sorafenib was a significant factor for achieving

long term sorafenib treatment over 1 year. Special caution must be paid for adverse events in case with longterm sorafenib treatment.

P1-75

Prognostic Impact of Clinical Factors of Sorafenib in Patients with Advanced Hepatocellular Carcinoma

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Background: We aimed to analyze the prognostic impact of baseline and early clinical markers in advanced hepatocellular carcinoma.

Methods: We prospectively studied 89 Japanese patients with hepatocellular carcinoma (Child-Pugh A, n = 59; Child-Pugh B, n = 30) who were started with sorafenib between May 2010 and July 2013.

Results: The median overall survival of Child-Pugh score 5, 6, 7 and ≥ 8 patients were 14.5, 11.1, 8.7 and 4.6 months, respectively. Child-Pugh score 6 had significantly longer OS than Child-Pugh score 7 ($P = 0.049$). Multivariate analysis identified macrovascular invasion (MVI), alpha-fetoprotein (AFP), Child-Pugh score and aspartate aminotransferase (AST) as baseline predictors of survival. However, extra hepatic metastasis (EHM) was not a significant prognostic factor. In addition, decrease in AFP level and development of hand-foot skin reaction (HFSR) within 4 weeks after sorafenib initiation were closely associated with favorable survival.

Conclusion: Clinical factors, such as MVI, AFP ≥ 400 , Child-Pugh B, and AST ≥ 3 times UNL at baseline predicted a poor OS in patients treated with sorafenib. Of note, EHM was not prognosis factor. Early AFP change and development of HFSR seem to be useful clinical predictors of survival.

P1-76

Sorafenib Improves the Outcome of BCLC Stage C Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombus Who Undergo Surgical Resection

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Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Patients diagnosed with HCC at an early stage (BCLC Stage 0, A) currently undergo surgical resection (SR), liver transplantation or percutaneous ablation. However, HCC recurrence after these therapies is still common. Patients at an intermediate stage (BCLC Stage B) undergo transarterial chemoembolization (TACE), while BCLC stage C patients with compensated liver disease are treated with the multikinase inhibitor, sorafenib, which is the only approved agent recommended by the American Association Study of Liver Diseases for HCC BCLC Stage C. Although data from two randomized controlled trials showed that sorafenib monotherapy prolonged overall survival (OS) and increased time to progression (TTP) in patients with advanced HCC, some BCLC stage C patients with Child-Pugh Class A liver function had better outcomes with SR compared to those who received sorafenib monotherapy. In this study, we evaluated whether sorafenib use after liver resection had an impact on tumor relapse and metastasis in BCLC stage C HCC.

Methods: This retrospective study enrolled 36 male HCC patients who were BCLC stage C Child-Pugh class A, and who underwent surgical resection at the First Affiliated Hospital of Kunming Medical University between January 2009 and December 2013. There were 24 patients in the SR group and 12 patients in the SR+sorafenib group. All patients had newly diagnosed, solitary large (>5 cm) tumors, and had received no prior therapy. Patients in the SR+sorafenib group received oral sorafenib (dose 200 mg-800 mg/d) within 30 days after surgery and the follow-up time period was ≥ 6 months. Patients with acute or chronic lesions in any other organs outside the liver, or metastases within 3 months after SR were excluded. Patients who received any treatments for HCC after surgical resection except sorafenib were excluded. The primary outcome was TTP (the time from surgical resection until HCC recurrence or extrahepatic metastases discovered by CT/MR). The secondary outcome was the rate of postoperative recurrence or metastasis. TTP and OS were analyzed using Kaplan Meier curves.

Results: Patients in the SR+sorafenib group had a significantly longer TTP compared to patients in the SR group [29 months (95% CI = 26.5, 31.5 months) vs. 22 months (95% CI = 18.0 to 26.0 months)] ($p = 0.041$). Patients in the SR+sorafenib

group also had a significantly longer median OS compared to patients in the SR group [37 months (95% CI = 34.8, 39.2 months) vs. 20 months (95% CI = 24.1, 36.0 months)] ($p = 0.01$). The SR group had 18 cases (75%) of recurrence/metastasis (14 cases of relapse, 2 cases of lung metastasis, 1 case of right adrenal metastasis and 1 case of thoracic bone metastasis). There were 6 cases (50%) of recurrence/metastasis in the SR+sorafenib group (5 cases of residual liver relapse and 1 case of lung metastasis). The most common adverse events in the SR+sorafenib group were skin reactions (91.67%), diarrhea (83.33%), and hypertension (83.33%), all of which were resolved with treatment.

Conclusions: Sorafenib after SR was well-tolerated in HCC BCLC stage C patients with Child-Pugh class A liver function. Patients who received oral sorafenib after SR had better outcomes compared to patients who received only SR. It is important to validate these data in multicenter, randomized controlled trials.

P1-77

Safety and Efficacy of Sorafenib Treatment in Chinese Patients with Prior Surgery or Unresectable Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Background: Hepatocellular carcinoma (HCC) is increasing worldwide, particularly in Asian-Pacific countries. Two randomized controlled trials (RCT) report that sorafenib, a multi-kinase inhibitor, provides survival benefits in HCC patients. This real-world study evaluated sorafenib safety and efficacy in Chinese patients with prior surgical resection or unresectable HCC (uHCC) with portal vein tumor thrombosis (PVTT).

Methods: A total of 338 Chinese patients from the international database of the GIDEON study were included in this analysis. Among all 338 patients receiving sorafenib therapy, 111 patients (32.8%) underwent prior surgical resection and

115 patients (34%) presented PVTT at study entry, respectively. Efficacy end points included response rate, overall survival, time to progression, progression-free survival and adverse events (AE).

Results: Patients who received prior HCC surgery had less advanced disease at baseline (initial sorafenib therapy) than others. The proportion of vascular invasion in patients with prior resection and those without prior resection was 12.6% vs. 27.8%, PVTT (17.1% vs. 42.3%), proportion of patients with TNM stage III or IV was 56.7% vs. 87.2%, BCLC stage C or D was 52.3% vs. 74.9%, Child-Pugh score B or C was 7.2% vs. 19.8%, and CLIP score 4 to 6 was 3.6% vs. 20.7%, respectively. HCC patients with PVTT had more advanced disease at baseline than those without PVTT, the proportion of patients with vascular invasion was 60% vs. 3.8%, TNM stage III or IV was 94.8% vs. 69.9%, BCLC stage C or D was 95.7% vs. 53.1%, and CLIP score 4 to 6 was 40.9% vs. 1.9%, respectively. The proportion of patients with prior surgery was less in patients with PVTT (16.5% vs. 42.6%). Generally AE profiles were consistent with those reported in the RCTs. AEs were more frequent in prior surgery group than in non-prior surgery group (57.7% vs. 46.8%). All-cause mortality was slightly higher in patients with PVTT than in those without PVTT (57.3% vs. 47.3%). Frequency of drug-related AEs, SAEs, and AEs resulting in permanent discontinuation was similar regardless of surgical or PVTT status. AE onset time was most often within 30 days of starting sorafenib therapy, then declined markedly. Time between initial diagnosis and sorafenib therapy was 6.6 months; range: 0.4–126 months for prior-surgery group and 0.7 (0–69.5) months for non-prior surgery group. The proportion of patients in prior-surgery group with TNM stage IV was 6.3% vs. 31.5%; proportion with BCLC stage C or D was 26.1 vs. 52.3% for at initial diagnosis vs. at start of sorafenib therapy, respectively. For tumor morphology, 18.0% vs. 57.7% had ‘multinodular’ tumor morphology, and 18.9% vs. 48.6% of patients having >3 lesions in liver at initial diagnosis and at initiation of sorafenib, respectively.

Conclusion: Various patterns are found in sorafenib use for HCC treatment in real-world clinical practice in China. The data indicate that sorafenib can be used without undue risk in Chinese uHCC patients receiving prior surgery or with PVTT presence, also AE onset declines markedly after first month. The higher proportion patients with more advanced HCC disease characteristics between initial HCC diagnosis and sorafenib treatment suggests that earlier use of sorafenib may maintain earlier disease stage and should be considered.

P1-78

GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of Its Treatment with Sorafenib): Final Clinical Findings in Chinese Patients

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Background: GIDEON is a global, prospective, non-interventional study conducted in 39 countries, including China, to evaluate the safety and efficacy of sorafenib in patients with unresectable hepatocellular carcinoma (uHCC) in real-life clinical practice, including Child-Pugh B and C patients with more advanced liver dysfunction. Here, we report data from the final analysis of patients from the Chinese subset of GIDEON.

Methods: Patients with uHCC, whose physicians had decided to treat them with sorafenib, under the approved labeling and prescribing guidelines, were eligible for inclusion. Demographic data and disease/medical history were recorded at entry. Sorafenib dosing and adverse events (AEs) were collected at follow-up visits.

Results: A total of 338 Chinese patients were available for intention-to-treat analysis of safety and efficacy. At the start of sorafenib therapy, 74% of patients had Child-Pugh A status and 15.1% Child-Pugh B status. Almost all Chinese patients (98.5%) received the approved 800 mg initial sorafenib dose, regardless of Child-Pugh status. The median duration of therapy was longer than in the global report. The incidence of AEs and drug-related AEs were slightly higher in Child-Pugh B patients. The most common drug-related AEs were diarrhea, hand-foot skin reaction (HFSR) and rash/desquamation. The majority of AEs occur within the first 30 days of treatment. Median overall survival (OS) was 322 days. The OS was longer in Child-Pugh A than in Child-Pugh B patients.

Conclusions: In Chinese patients, the overall dosing strategy was consistent across Child-Pugh subgroups. Although sorafenib was well tolerated, AEs were more common in patients with worse liver function. Child-Pugh status appears to be a useful prognostic factor for OS.

P1-79

Sorafenib Treatment in Elderly Patients with Hepatocellular Carcinoma

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Purpose: Sorafenib is the standard treatment for advanced hepatocellular carcinoma (HCC). Recently, HCC patients around 80 years increase. We aimed to evaluate safety and efficacy of sorafenib in the elderly population.

Methods: We retrospectively reviewed data from patients treated with sorafenib for HCC at our group. We compared safety and efficacy data across different age groups.

Table 1. Treatment-emergent adverse events (AEs) by Child-Pugh status (for Abstract P1-78)

%	Child-Pugh A (n = 246)	Child-Pugh B (n = 48)	Child-Pugh C (n = 2)	Total* (n = 331)
AEs (all grades)	124 (50.4)	27 (56.3)	0	167 (50.5)
Drug related AEs (all grades)	67 (27.2)	17 (35.4)	0	95 (28.7)
Serious AEs (all grades)**	58 (23.6)	12 (25.0)	0	77 (23.3)
Drug-related serious AEs (all grades)	0	1 (2.1)	0	1 (0.3%)
All grade 3 or 4	14 (5.7)	4 (8.3)	0	20 (6.0)
Drug related grade 3 or 4	9 (3.7)	2 (4.2)	0	12 (3.6)
AEs resulting in permanent discontinuation of sorafenib	22 (8.9)	5 (10.4)	0	29 (8.8)
Deaths***	127 (51.6)	27 (56.3)	0	166 (50.2)

*Includes 35 non-evaluable patients.

Results: Since 2009, 254 patients were treated, 192 (75.6%) were <80 years old and 62 (24.4%) were ≥80. The frequency of a response rate (13.0 vs. 16.7%) and a tumor control rate (48.8% vs. 64.5%) was similar between the two groups. The frequency of dose reduction (64.5 vs. 47.6%) was similar between the two groups. The frequency of toxicities was similar between the two groups: liver dysfunction (15.1% vs. 22.6%), bleeding (11.0% vs. 8.1%), hand-foot skin reaction (55.2% vs. 53.2%), diarrhea (16.1% vs. 12.9%) and hypertension (20.8% vs. 24.2%). The frequency of interruption of treatment and definitive discontinuation of treatment due to toxicity reduction was similar between the two groups. There was a trend toward less frequent of treatment after sorafenib in the elderly group (33.9% vs. 22.4%) and significantly less frequent of local treatment with sorafenib in the elderly group (25% vs. 8.1%) ($P = 0.0043$). Median progression-free survival was 3.9 months in the younger age and 3.1 months in the elderly group ($P = 0.0202$), while median overall survival was 9.7 months in the younger age and 8.7 months in the older age group.

Conclusion: Sorafenib showed similar results in terms of safety and efficacy in the elderly and younger HCC populations. Sorafenib treatment is a reasonable option in fit elderly patients presenting with advanced HCC.

P1-80

Withdrawn

P1-81

A Phase 1B Study of 5-Fluorouracil, Folinic Acid and Oxaliplatin (FOLFOX4) Plus Ramucirumab in Patients with Advanced Hepatocellular Carcinoma

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Background: Advanced hepatocellular carcinoma (HCC) has a dismal prognosis, with a median survival time of 3 to 4 months with supportive care in East Asian countries. FOLFOX4 is systemic treatment options for advanced HCC in Asia. Ramucirumab (RAM) is a recombinant human monoclonal antibody that specifically binds with high affinity to the extracellular domain of vascular endothelial growth factor

receptor-2 (VEGFR-2), inhibiting its activation by VEGF ligands. Preliminary evidence of RAM anticancer activity in the 1st-line treatment of unresectable HCC was suggested in a single-arm, phase 2 study in Western patients. An acceptable safety profile of RAM in combination with FOLFOX regimens was demonstrated in colorectal and esophagogastric cancer in two phase 2 studies (Garcia-Carbonero et al., *The oncologist* 19: 350–351, 2014).

Methods: This multicenter, single-arm, open-label, phase 1b study was designed to investigate the safety and tolerability of RAM in combination with FOLFOX4 in patients with advanced HCC. Asian patients with advanced HCC who have not received previous systemic chemotherapy or molecular targeted therapy for the treatment of HCC, and have at least 1 measurable or nonmeasurable lesion, a Child-Pugh score of ≤6, Barcelona Clinic Liver Cancer stage C or B not amenable or refractory to locoregional therapy, have adequate marrow and organ function and a performance status of 0-1 on the Eastern Cooperative Oncology Group scale are eligible for this study. Patients will receive RAM 8 mg/kg intravenously (IV), Day 1 and FOLFOX4 [oxaliplatin 85 mg/m² IV, Day 1; folinic acid 200 mg/m² IV, Day 1 and 2; fluorouracil (FU) IV bolus 400 mg/m², Day 1 and 2 and FU 600 mg/m² as a 22-h continuous infusion, Day 1 and 2] every 2 weeks. The primary endpoint of this study is to determine if the recommended dose of RAM (8 mg/kg IV, every 2 weeks) may be safely administered to patients with advanced HCC in combination with FOLFOX4. Secondary endpoints include pharmacokinetics and immunogenicity of RAM as well as safety and antitumor activity of RAM in combination with FOLFOX4. The study plans to enroll 6 to 9 patients. The maximum acceptable dose-limiting toxicity rate is 22% (2/9). As of Feb 28, 2015, 5 patients have been enrolled in 3 sites in Taiwan. The trial has been registered under the number NCT02069041.

P1-82

Real Life Hepatocellular Carcinoma (HCC) Patients Data with Sorafenib Treatment in Dharmas National Cancer Hospital Indonesia Period 2008–2010

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Background: Sorafenib was launched in 2007 for unresectable Hepatocellular Carcinoma (HCC), this drug still becomes the only approved systemic therapy for HCC treatment. No specific data obtained from Indonesia about HCC patients treatment with Sorafenib. Dharmas National Cancer Hospital in Jakarta, is one of National government hospitals received many referral patients throughout Indonesia. Reported of 105 HCC cases in Dharmas Cancer Hospital,

where thirty-two of them treated with Sorafenib in period 2008–2010.

Objective: This study was aimed to evaluate characteristic, duration of treatment (DOT), and safety from these real life patient data using Sorafenib in Dharmas National Cancer Hospital, Indonesia.

Method: This was a retrospective study from 2008–2010. Patients who died or lost follow up within 1 month of Sorafenib treatment were excluded from analysis because this may represent the loose patients' compliance for treatment. DOT is counted from initial Sorafenib intake until they died or lost to follow up with the treating doctor. Statistical analysis was done using the software SPSS version 17.0.

Results: A total 105 HCC cases in Dharmas National Cancer hospital from 2008 to 2010 with staging BCLC-B and C; eighty-two (78.09%) among all HCC patients were men. Thirty-two (30.5%) patients treated with Sorafenib mostly using 400 mg/day. Unfortunately, twelve (37.5%) patients died and/or lost to follow up within 1 month; most reasons are patients were back to their home towns. The median DOT for the rest 20 patients was 6.38 months (95% confidence interval [CI], 5.18–7.56 months) (in period of following up with the treating doctor). Patients characteristic with Non B non C have better DOT compared with Hepatitis B and Hepatitis C patients, was 7.7 months, 5.4 months, and 5.5 months respectively. Thirteen patients were Child Pugh-A had DOT of 7.8 months compared with Child Pugh B patients DOT were 5.4 months. One patient reported still use Sorafenib until death in 2012, with longest DOT and OS was 40.6 months. Sorafenib generally could be tolerated by the patients. The most common adverse events are mild or moderate, such as hand and foot skin reaction and diarrhea.

Conclusion: Sorafenib still becomes the only approved systemic therapy in HCC. After being launched in 2007, many patients gain benefit in using Sorafenib. Median DOT was 6.38 months (This result was good, compared with OS reported in AP study with Overall Survival (OS) Sorafenib vs. Placebo was 6.5 months vs. 4.2 months). Mostly patients in Dharmas Cancer hospital were referral patients throughout Indonesia, since the wide and large Indonesia coverage may influence patients' compliance to follow up with the treating doctors.

P1-83

Comparison of Outcome of Hepatic Arterial Infusion Chemotherapy Versus Sorafenib Monotherapy in Patients with Advanced HCC

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Background & Aim: Sorafenib is currently the only standard treatment for advanced HCC, though the response rate remains poor (4%). We compared the overall survival after hepatic arterial infusion chemotherapy (HAIC) versus sorafenib monotherapy for advanced hepatocellular carcinoma (HCC).

Methods: This retrospective study enrolled 208 patients with advanced HCC and Child-Pugh A but without extrahepatic metastasis. Patients were divided into the HAIC group (n = 144, treated with HAIC) and sorafenib group (n = 64, treated with sorafenib), and followed to death or withdrawal of therapy. Response to treatment and overall survival were compared.

Results: The proportion of patients who showed complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD) were 6/25/41/21% and 2/2/44/42% in the HAIC and sorafenib groups, respectively. The response rate was higher in HAIC group (31%) than sorafenib group (4%). The MST was 10 months in both HAIC and sorafenib groups. There was not difference of overall survival in both HAIC and sorafenib groups. In patients with macroscopic vascular invasion (MVI), the response rate was higher in the HAIC group (31%) than sorafenib group (0%). The tendency of survival was better in the HAIC group (9.7 months) than sorafenib group (4.3 months, $p = 0.024$) Multi-variate analysis identified MVI (hazard ratio 2.1, $p = 0.024$) as a significant and independent determinant of survival in the sorafenib group.

Conclusions: The response rate of HAIC was higher than that of sorafenib monotherapy. HAIC responder could obtain the favorable prognosis despite MVI. For the 1st line for advanced HCC patients without extrahepatic metastasis, HAIC might be desirable.

P1-84

Phase 1 Study of PV-10 for Chemoablation of Hepatocellular Cancer and Cancer Metastatic to the Liver

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Background: Intralesional PV-10, a 10% solution of rose bengal, has recently demonstrated high rates of complete response and durable local control in metastatic melanoma. The current Phase 1 study is assessing safety, pharmacokinetics, and preliminary efficacy of PV-10 in subjects with non-resectable hepatocellular carcinoma or cancer metastatic to the liver.

Method: Subjects having at least one liver tumor ≥ 1 cm are administered a single percutaneous intralesional injection of PV-10 to one Target Lesion at dose of 0.25 or 0.50 ml per cm³ lesion volume. Plasma concentrations of PV-10 from 1 hour to 28 days after injection are measured. Radiologic assessments of the injected Target Lesion are performed to determine response over initial 28 day and long-term 9–15 month periods. Serum levels of potential liver injury markers are measured, and adverse events recorded.

Results: In an initial study cohort, six subjects received PV-10. Significant adverse events were limited to injection site and photosensitivity reactions, and resolved without sequelae. All injected tumors were stable in size at 28 days, and of 4 that had long-term assessment, 2 had partial response, for a long-term tumor-specific objective response rate of 50%. PV-10 plasma levels decreased rapidly in a bi-exponential pattern, with initial and terminal phase half-lives of 4.5 and 100 hours, respectively. Elevated liver enzymes levels subsided within a week of treatment.

Conclusion: Preliminary efficacy in treatment of liver tumors with PV-10 was observed. Toxicity was transient, and treatment had acceptable tolerability. The study is continuing at three study centers with two expansion cohorts to assess response in hepatocellular carcinoma and other cancers metastatic to the liver.

P1-85

A Clinical Validation Study of FGF4 FISH and Copy Number Assay to Predict Sorafenib Response

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We previously reported that gene amplification of *FGF3/FGF4* is a predictive marker for sorafenib hyper-responder of hepatocellular cancer. *FGF3/FGF4* fluorescence in situ hybridization (FISH) is expected to be a powerful tool for screening these population with various types of cancers. In this study, we have prepared the FISH probe for *FGF4* (11q13.3) and validated the probe performance using 24 clinical samples. A cell line and peripheral blood mononuclear cells were used for the positive and negative controls. *FGF4* and *CEN11p* probes were successfully hybridized to the amplification positive KYSE220 cells. Next, we evaluated 24 formalin fixed paraffin embedded (FFPE) tumor tissues from esophageal cancer patients. Scoring and cut-off-definition were done according to the ASCO/CAP recommendations for *HER2* testing. The eighteen samples were judged as FISH positive (*FGF4/CEN11p* ratio >2.0) with cluster formation and other samples were judged as negative. DNA copy numbers of *FGF4* in the tumors was determined by Taqman copy number assay. Copy number assay judged the 18/24 cases as positive when the cut-off value was set at 4.0. Concordance rate between FISH and the copy number assay was 83% (20/24). Discrepancy between two assays (FISH ratio <2.0 and copy number >4.0) was detected in two cases. These results suggest that FISH as well as copy number assay is feasible for clinical FFPE tumor samples for the screening of *FGF3/FGF4* abnormality. The FISH assay will be available in the CRO for the prescreening of the multi-kinase inhibitors.

P1-86

Clinical Factors for Predicting the Response of Sorafenib in Hepatocellular Carcinoma with Lung Metastasis

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Background: Lung is the most common site of extrahepatic metastasis in hepatocellular carcinoma (HCC). Among available modalities, sorafenib is currently the only standard therapy, but its response rate is relatively low (0.7~3%). The objective of this study is to investigate clinical factors that would predict the response of sorafenib before use for lung metastasis in HCC.

Methods: Between 2011 and 2012, we investigated 19 consecutive patients who were prescribed sorafenib for HCC with lung metastasis. The 19 patients were categorized into two groups according to time to progression of 2.4 months based on previous studies: sorafenib responder and non-responder. Clinical characteristics of the patients were analyzed at the time of using sorafenib. Tumor response was evaluated by modified RECIST criteria.

Results: One patient achieved complete response who had only lung metastatic lesion and 5 patients achieved partial response or stable disease for at least 3.3 months. The median time to progression of these 5 patients was 6.3 months in terms of lung metastasis. These 6 patients (31.58%) were categorized as a sorafenib responder group. The other 13 patients (68.42%) were non-responder and their lung metastasis showed progressive disease in the next response evaluation usually done in about 2 months. The level of AFP and PIVKA-II before using sorafenib were significantly different (AFP 50.0 ± 55.6 , 43682.8 ± 60039.1 , PIVKA-II 128.3 ± 161.7 , 15049.8 ± 21529.6 , $p = 0.022$, 0.028 , responder, non-responder, respectively) between the two groups. Controlling intrahepatic lesion (complete, partial response and stable disease) and tumor burden of lung metastasis showed no significant differences in our data.

Conclusion: Relatively low level of tumor markers before using sorafenib is significantly associated with the treatment response of HCC with lung metastasis to sorafenib. Further study is necessary in more recruited number of patients.

P1-87

Molecular Target Drug (Sorafenib) Might Cause the Activation of Kupffer Cell

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Background: We have already reported that molecular target drug Sorafenib (SF) might lead apoptosis by increasing serum TNF-alpha and decreasing soluble Fas in treatment for advanced hepatocellular carcinoma (Cancer Chemother Pharmacol 73:223–229, 2014). It has reported that Kupffer cells phagocytosed contrast agents and they were responsible for the delayed images of contrast ultrasound in the liver (Yanagisawa K, et al: Ultrasound Med Biol 33:318–325, 2007). In contrast enhanced ultrasonography (CEUS) using sonazoid, the distance of collapsed micro-bubble might reflect the function of Kupffer cells.

Aim: The aim of this study was to clarify whether SF influence to the distance of collapsed MB in patients with liver cirrhosis (LC) and advanced hepatocellular carcinoma (aHCC).

Patients/Methods: Ten adult Japanese LC patients who had aHCC were treated with SF between September 2009 and February 2015. Blood samples were collected in the early morning before and 4 weeks after treatment. TNF-alpha were measured using an enzyme immunoassay (EIA), soluble Fas ligand (sFas-L), soluble TNF-receptor (aTNF-R) and soluble Fas (sFas) were measured using enzyme-linked immunosorbent assay (ELISA). Patients were underwent CEUS using sonazoid before and after treatment of SF. The distance of collapsed MB in the post-vascular phase (Kupffer phase) was measured in the right hepatic lobe were collapsed by a flash-replenishment after 10 minutes from the injection of the contrast agent.

Results: Three patients had HBV-related LC, 4 patients had HCV-related LC, and 3 patients had non-B, non-C LC. Six patients had Child-Pugh class A and 4 patients had class B. There were 9 patients with stage IVA disease and one patient with stage IVB disease. In therapeutic effects, 9 patients showed SD and one patient showed PD. The serum levels of TNF-alpha significantly increased treatment and the serum levels of sFas significantly decreased after SF treatment. There was significant difference in the distance of collapsed MB between before and after SF treatment in LC patients with aHCC. Furthermore, there were negative correlation between the distance of collapsed MB and serum levels of TNF-alpha.

Conclusions: In LC patients with aHCC, the treatment of SF might induce the increasing of serum levels of TNF- α and these changes might indicate the activation of Kupffer cells.

P1-88

Withdrawn

P1-89

Phase II Trial Comparing the Oral c-Met Inhibitor Tepotinib (MSC2156119J) with Sorafenib First Line in Asian Patients with Advanced HCC

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Background: HCC is a poor-prognosis disease for which the only approved therapy is sorafenib. However, this is not widely used in Asia, creating an unmet medical need. Mesenchymal-epithelial transition factor (c-Met) receptor amplification/overexpression in patients with advanced HCC is associated with tumor aggressiveness. The highly selective c-Met inhibitor tepotinib (MSC2156119J) has demonstrated promising antitumor activity in a phase I trial involving 143 patients with solid tumors, particularly in patients with c-Met-positive disease. The maximum tolerated dose of tepotinib was not reached at a dose of 1,400 mg/day and pharmacokinetic/pharmacodynamic modelling was used to identify a recommended phase II dose (RP2D) for tepotinib of 500 mg/day. This RP2D of tepotinib was also shown to be well tolerated Asian patients in the phase Ib part of this trial. We describe the design of the phase II part of the trial in which tepotinib 500 mg/day will be compared with sorafenib as first-line therapy for advanced HCC (NCT01988493).

Trial Design: The phase II part will be a randomized, open-label, active-controlled trial that will be conducted at 30–35 sites in mainland China, South Korea, Taiwan, and other Asian countries. Eligible patients will be adults with histologically/cytologically confirmed, measurable advanced HCC of Barcelona Clinic Liver Cancer Stage C and will have Child-Pugh Class A liver function without encephalopathy. In

addition, eligible patients will have ECOG performance status 0–2 and will not have received prior systemic therapy for HCC. All patients will have c-Met-positive tumors, defined as c-Met protein overexpression, ie, moderate (2+) or strong (3+) staining for c-Met in the majority ($\geq 50\%$) of tumor cells using immunohistochemistry. A planned 140 patients will be randomized to receive first-line tepotinib 500 mg/day or sorafenib 400 mg BID over a 21-day cycle. The minimum duration of treatment will be one cycle, with therapy administered until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint is to evaluate efficacy as measured by time to progression. Secondary endpoints include safety, tolerability, and antitumor activity. Patients will be followed for survival every 3 months after completion of therapy. Exploratory objectives include patient-reported outcomes, assessed using Functional Assessment of Cancer Therapy Hepatobiliary (FACT-HP) and association of potential biomarkers with prognosis and tepotinib activity. This large randomized phase II trial will provide the first evidence regarding whether tepotinib represents an effective alternative to sorafenib for the first-line treatment of Asian patients with c-Met-positive advanced HCC.

P1-90

Phase Ib Data for the Oral c-Met Inhibitor Tepotinib (MSC2156119J) in Asian Patients with Advanced HCC: Confirmation of the Recommended Phase II Dose

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Background: Mesenchymal-epithelial transition factor (c-Met) receptor overexpression in patients with advanced HCC is associated with tumor aggressiveness in what is a generally poor prognosis disease. Furthermore, sorafenib, the only approved therapy for HCC, is not widely used in Asia, creating an unmet medical need. Tepotinib (MSC2156119J) is a highly selective c-Met inhibitor that has demonstrated promising antitumor activity in a phase I trial, particularly in patients with c-Met-positive tumors. Data from this trial and preclinical data were modelled to identify a recommended phase II dose (RP2D) of tepotinib of 500 mg/day. We report data from the phase Ib part of a phase Ib/II trial of tepotinib as first-line therapy for advanced HCC (NCT01988493).

Table 1. (for Abstract P1-90)

Characteristic	(n = 20)
Median age, years (range)	57.0 (50.0–63.5)
Male/female (n)	17/3
ECOG performance status 0/1 (n)	9/11
Median prior systemic therapies, n (range)	2 (1–5)
<i>Treatment-emergent adverse events (TEAEs)</i>	
≥1 TEAE (n)	19/20
Dose-limiting toxicity (n)	0
Tepotinib-related TEAEs occurring in >3 patients (n)	
Diarrhea	7
Nausea	4
Fatigue	3
Aspartate transaminase elevation	3
Pruritus	3
Grade 3/4 tepotinib-related TEAEs (n)	
Grade 3 lipase elevation	2 (both treated with tepotinib 500 mg/day)
Grade 3/4 hypertension, ALT and AST increase, hyponatremia, and hyperuricemia	1 (treated with tepotinib 300 mg/day)

Methods: Adults with confirmed, advanced HCC of BCLC Stage C, Child-Pugh Class A liver function without encephalopathy, and ECOG status 0–2 were recruited in China, South Korea, Taiwan, and other Asian countries. The open-label, single-arm phase Ib part had a 3+3 dose-escalation design (tepotinib 300 or 500 mg p.o./day; 21-day cycle), with 12 patients (pts) to be enrolled at the RP2D (total enrolment of up to 18 pts). All patients had to provide a tumor biopsy for determination of c-Met status at study entry, but Met+ status (c-Met protein overexpression of 2+/3+ on immunohistochemistry) was not required for the phase Ib part.

Results: Twenty pts have been enrolled. Six pts received tepotinib 300 mg/day; 14 received tepotinib 500 mg/day. Patient characteristics and safety data are shown in the table. No dose-limiting toxicities were observed, meaning that the RP2D is 500 mg/day.

Conclusions: The reported safety data from the phase Ib part of this phase Ib/II trial have confirmed the RP2D of tepotinib as being 500 mg/day in Asian pts with advanced HCC. Safety and the tolerability profile were similar to those observed in previous trials of tepotinib. Enrolment to the phase II part of the trial, in which pts will be randomized to receive tepotinib 500 mg/day p.o. or sorafenib 400 mg twice-daily p.o., will start in 2015.

P1-91

Computed Tomography Response Criteria in Patients with Advanced Hepatocellular Carcinoma Receiving Anti-Angiogenic Therapy in Clinical Trials

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Background: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 is widely used for tumor response assessment in patients with advanced hepatocellular carcinoma (HCC). This study explored the value of different computed tomography (CT) response criteria in predicting overall survival (OS) of patients with advanced HCC receiving anti-angiogenic systemic therapy in clinical trials.

Methods: A retrospective blinded analysis of CT scans was performed by two independent radiologists (R1 and R2). Three CT response criteria were used: RECIST 1.1, modified RECIST (mRECIST; restricting measurements to arterially enhanced parts of the tumors), and Choi criteria (defining a partial response as a 15% or more reduction in tumor density or a 10% or more reduction in tumor size). The anti-angio-

Table 1. Tumor responses based on common criteria for each radiologist (n = 39) (for Abstract P1-91)

	RECIST 1.1		mRECIST		Choi criteria	
	R1	R2	R1	R2	R1	R2
PR (%)	2 (5)	3 (8)	7* (18)	5 (13)	19 (49)	16 (41)
SD (%)	31 (79)	25 (64)	22 (56)	30 (77)	10 (26)	10 (26)
PD (%)	6 (15)	11 (28)	10 (26)	4 (10)	10 (26)	13 (33)
Inter-radiologist agreement (%)	31 (79)		26 (67)		28 (72)	
Weighted κ	0.537		0.359		0.565	

PR = Partial response; SD = stable disease; PD = progressive disease; R1 = radiologist #1; R2 = radiologist #2.

*one patient achieved complete tumor response.

genic systemic therapy included sorafenib + UFUR, thalidomide + UFUR, bevacizumab+capecitabine, and bevacizumab + erlotinib. OS was calculated according to Kaplan-Meier method.

Results: A total of 39 patients were enrolled for the image analysis. Median OS was 6.1 months (range 1.4–82.1 months). The response measurements by the 2 radiologists were summarized in the accompanying table. The inter-radiologist agreement rates were 79%, 67%, and 72% by RECIST 1.1, mRECIST, and Choi criteria, respectively. Tumor progression defined by RECIST 1.1 (R1: hazard ratio[HR], 3.082; P = 0.003; R2: HR, 3.642; P = 0.008), HBV infection, AFP >400 ng/dl, and major vascular invasion were identified as potential predictors of poor OS in the univariate analysis. Responses determined by mRECIST or Choi criteria were not consistent between the 2 radiologists in predicting OS.

Conclusion: Although inter-observer agreement rates are similar for each of the 3 imaging criteria, tumor progression determined by RECIST 1.1 appears to be most consistently correlated with OS.

P1-92

Elevated Serum Levels of M2BPGi Predict the Burned Out NASH and Hepatocellular Carcinoma with Non-Alcoholic Steatohepatitis

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Background: Recently, the novel sugar chain marker WFA+M2BP (M2BPGi) has attracted attention as a potentially useful non-invasive liver fibrosis marker, and reported high levels of M2BPGi is high risk of hepatocellular carcinoma

(HCC) with hepatitis C. We reported the usefulness of M2BPGi as a marker of fibrotic change in the diagnosis of progression of fibrosis NASH (Hepatology 60,129A,2014). We have assessed M2BPGi in NAFLD (non alcoholic fatty liver disease) cases and examined its utility as prediction of burned out NASH (non-alcoholicsteatohepatitis) and HCC.

Methods: We assessed M2BPGi in 294 NAFLD patients at who had undergone liver biopsies (mean age: 54.2 ± 14; M/F: 149/145; F0/1/2/3/4:24/87/65/87/31). In addition to its utility in diagnosing fibrosis in NASH, we examined the associations of M2BPGi to fibrosis stage. Moreover, M2BPGi of burned NASH cases and non-burned out NASH in cirrhosis with NASH, and HCC cases and non HCC cases was measured. Measurement of glycosylation isomer of Mac-2 binding protein (M2BPGi) in serum. This kit measures glycosylation isomer of Mac-2 binding protein based on the chemiluminescence enzyme immunoassay method with CDP-StarR chemiluminescent substrate. This kit is exclusively designed for Automated Immunoassay System HISCL-series.

Results: M2BPGi increased as fibrosis progressed (P < 0.0001). Specifically, M2BPGi was significantly higher in F3 and F4 than in F0-2 (0.8 vs. 1.23; P < 0.0001), the cutoff value was 1.01, the AUC was 0.70, sensitivity was 68.4%, specificity was 70%, PPV was 60%, and NPV was 77.5%; thus, M2BPGi was useful in diagnosing NASH with progression of fibrosis. Among cirrhotic liver, M2BPGi was higher with burned out NASH in which cirrhosis than nonburned out NASH (6.5 vs1.8, p = 0.0031). Furthermore the HCC cases (n = 13) had significantly high levels of M2BPGi compared with the non HCC cases (n = 281) (6.5 vs. 1.8, p < 0.0001).

Conclusion: Assessment of M2BPGi in NAFLD was considered useful in predicting advance fibrosis in NASH, as well as therapeutic effects. Specially, M2BPGi is useful for predicting a burned out NASH and future of HCC with NASH.

P2-01

Multi-Analyte Analysis of Serum Cytokines to Predict Treatment Outcome in Patients with Hepatocellular Carcinoma Treated with Radiotherapy

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Background: Cytokine, which is involved in chronic inflammation and also related with tumor aggressiveness and resistance to treatment in many cancers. However, the significance of cytokines has been investigated limitedly about in tumor response of radiotherapy (RT). The aim of this study was to analyze the serum cytokine levels and identify the significance of the serum cytokines on treatment outcome in patients with hepatocellular carcinoma (HCC) treated with RT.

Methods: In this prospective study, patients with HCC who treated with RT were eligible. Blood samples were collected before and after completion of whole RT course. Serum cytokine levels measured using Cytokine Bead Array kits were analyzed with patients' clinical profiles and treatment responses.

Results: Between September 2008 and October 2009, 51 patients were included in analysis. Median follow-up duration was 12.3 months (range, 0.5–62.3). Forty-seven patients were diagnosed as modified UICC stage III or IV at timing of RT. Baseline serum IL-8 level increased as stage increased and IL-6 level was high in patients with pre-RT treatment history (treatment-non-naïve). Higher baseline serum IL-6 level was observed in patients with treatment failure including overall, infield, and outfield failure than those without treatment failure. In subgroup analysis, the significant difference of serum IL-6 level was observed only in treatment-non-naïve comparing to treatment-naïve patients. Median overall survival and progression-free survival (PFS) were 13.9 and 7.7 months, respectively. Elevated serum IL-6 level was significantly associated with PFS for infield failure (HR 1.011, $p < 0.0001$).

Conclusions: The current findings suggest that the assessment of baseline serum IL-6 level may be helpful to predict treatment outcome after RT for HCC, especially in patients who had treatment history before RT.

P2-02

The T-Box Transcription Factor Eomesodermin Control NK and NKT Cells Activity and Favors Good Outcome in Hepatocellular Carcinoma After Resection

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Background: An efficient cytolytic T cell function is essential for immune mediated clearance of human hepatocellular carcinoma (HCC). However, the molecular mechanisms controlling transcription factor driving T cell mediated cancer rejection are still poorly understood. Here, we assessed the role of the T-box transcription factor eomesodermin (also known as eomes) in HCC.

Methods: The association between eomes positive cells and the clinical outcomes was assessed by immunohistochemistry (IHC) in a HCC patient cohort ($n = 331$). The expression of eomes in immune cells was assessed by flowcytometry.

Results: IHC showed decreased infiltration of eomes positive cells in tumoral tissues compared with paired peritumoral tissues. The counts of eomes positive cells in intra- and peri-tumoral tissues were negatively correlated with tumor size. Survival analysis showed that the levels of intra- and peri-tumoral eomes positive cells were related to overall survival (OS) in univariate analysis, and peri-tumoral eomes positive cells were related to OS in multivariate analysis ($P = 0.028$, H.R. [95% CI] = 0.569 [0.354–0.914]). Furthermore, the levels of peri-tumoral eomes positive cells showed independent prognostic value for OS in Barcelona Clinic Liver Cancer (BCLC) stage A patients ($P = 0.006$, H.R. [95% CI] = 0.507 [0.324–0.794]). Flowcytometry analysis showed no significant difference in the percentages eomes positive cells between intra- and peri-tumoral tissues among CD3⁺CD56⁺ NKT cells, CD3⁺CD56⁺ NK cells, CD4⁺ T cells and CD8⁺ T cells. However, we found that eomes MFI were down-regulated in NKT and NK cells in intra-tumoral tissues compared with peritumoral. In addition, perforin and granzyme-B were mainly expressed in eomes positive cells.

Conclusion: Eomes control cytotoxic activity of NKT and NK cells, peri-tumoral eomes is an independent prognostic indicator for early HCC patient after radical resection.

P2-03

Macrophage Colony-Stimulating Factor Expressed in Non-Cancer Liver Tissues Provides a Predictive Power for Recurrence in Patients with Hepatocellular Carcinoma

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Aim: This study was to investigate the role of macrophage colony-stimulating factor (M-CSF) in patients with hepatocellular carcinoma (HCC) after resection.

Patients and Methods: Expression of M-CSF, distribution of macrophages (Mfs) and CD163-positive M2Mfs, and angiogenesis were assessed in liver tissues containing paired tumors and peritumoral regions. Prognostic values of these and other clinicopathologic factors were evaluated. Hepatic Mfs or the monocytes were isolated from mice and cultured with media containing M-CSF. The concentration of vascular endothelial growth factor (VEGF) in media was assessed. Furthermore, the role of the M-CSF-induced hepatic Mfs on proliferation of the vascular endothelial cell (VEC) was investigated.

Results: A strong correlation between the expressions of M-CSF and CD163 was observed in the peritumoral area. Also, groups with high density of M-CSF, CD163 or CD31 showed a significantly shorter time to recurrence (TTR) than low density groups. Multivariate analysis revealed the expression of M-CSF or hepatic M2Mfs in the peritumoral area as the most crucial factor responsible for shorter TTR. Moreover, the expression of M-CSF and hepatic M2Mfs in the peritumoral had better predictable power of the overall survival. Although values of VEGF increased both in media from both hepatic Mfs and monocytes incubated with M-CSF in a time- and dose-dependent manner, they were significantly greater in the hepatic Mfs compared with the monocytes. Proliferation of the VEC was the greatest in the cells co-cultured with the hepatic Mfs when M-CSF was present in media.

Conclusions: M-CSF increases hepatocarcinogenesis, most likely by inducing an angiogenic factor derived from the hepatic Mf stimulated by M-CSF. Furthermore, M-CSF could be a useful target for postoperative adjuvant therapy against HCC.

P2-04

Correlation Analysis of Discoidin Domain Receptor 2 Expression and Prognosis of Hepatocellular Carcinoma After Surgical Resection

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Background: Discoidin domain receptors (DDR2) have recently been identified as tyrosine kinase receptors for collagen, a key constituent of the extracellular matrix. Our previous study demonstrated that the suppression of DDR2 inhibited the growth of hepatocellular carcinoma (HCC) cells in a cell-type dependent manner. In this study, we analyzed the correlation of DDR2 expression with the prognosis of HCC patients with resection.

Methods: Between January 2008 and December 2009, 143 patients were clinically diagnosed with HCC and underwent surgical resection as initial treatment at the National Cancer Center, Korea. After application of Institutional Review Board requirement and exclusion criteria, 76 patients were enrolled. We performed quantitative, real-time polymerase chain reaction assays of DDR2 mRNA in HCC and surrounding non-tumor tissue from paraffin blocks of resected specimens. The increased DDR2 fold change (increase) and the decreased DDR2 fold change (decrease) were defined as 1^3 or $1 < \text{DDR2 value of tumor tissue} / \text{DDR2 value of surrounding non-tumor tissue}$, respectively.

Results: There were 13 patients (17.1%) in the increase group, and 36 patients (47.4%) in the decrease group. Between two groups, no significant difference was found in age at diagnosis, sex, etiology, mUICC stage, vascular invasion, Barcelona Clinic Liver Cancer (BCLC) stage, Child Pugh scores, albumin, total bilirubin, prothrombin time, or alpha fetoprotein; however, the increase group significantly showed smaller tumor size ($p = 0.033$), higher 3-year disease-free survival (DFS) rate ($p = 0.028$), longer 5-year overall survival (OS) time ($p = 0.037$), and higher 5-year OS rate ($p = 0.044$). However, Kaplan-Meier curves for 5-year OS showed marginally non-significant difference ($p = 0.051$).

Conclusions: The expression of DDR2 in HCC and surrounding non-tumor tissue might be a prognostic factor in patients with surgical resection, but we have not yet fully proven its significance. Further studies are needed in the future.

P2-05

A Novel and Validated Inflammation Based Score (IBS) Derived from Neutrophil to Lymphocyte Ratio Predicts Survival in Patients with Hepatocellular Carcinoma Following Curative Surgical Resection

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Background & Aims: As chronic inflammation is involved in the pathogenesis of hepatocellular carcinoma (HCC), we investigated the prognostic accuracy of a cluster of inflammatory scores, including the Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), platelet to lymphocyte ratio (PLR), Prognostic Nutritional Index (PNI), Prognostic Index (PI) and a novel Inflammation Based Score (IBS) integrated preoperative and postoperative neutrophil to lymphocyte ratio (NLR) in two independent cohorts. Further, we aimed to formulate an effective prognostic nomogram for HCC after hepatectomy.

Methods: Prognostic value of inflammatory scores and Barcelona Clinic Liver Cancer (BCLC) stage were studied in a training cohort of 772 patients with HCC underwent hepatectomy. Independent predictors of survival identified in multivariate analysis were validated in an independent set of 349 patients with an overall similar clinical feature.

Results: In both training and validation cohorts, IBS, microscopic vascular invasion and BCLC stage emerged as independent factors of overall survival (OS) as well as IBS, microscopic vascular invasion, BCLC stage, and AFP emerged as independent predictors of recurrence-free survival (RFS). The predictive capacity of the IBS in both OS and RFS appeared superior to that of the other inflammatory scores in terms of C-index. Additionally, the formulated nomogram comprised IBS resulted in more accurate prognostic prediction compared with BCLC stage alone.

Conclusions: IBS is a novel and validated prognostic indicator of HCC after curative resection, and a robust HCC nomogram including IBS was developed to predict survival for patients after hepatectomy.

P2-06

Modifiable Prognostic Factors in Patients with Hepatocellular Carcinoma Underwent Non-Surgical Treatment

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Backgrounds: Prognostic factors of HCC, such as liver function reserve, tumor status and alpha-fetoprotein, are well-known. However, most of them can not modified. In this retrospective outcomes research, we studied modifiable or interventional factors of HCC underwent non-surgical treatment.

Methods: From 2002 to 2012, all HCC met inclusive criteria were recruited. Inclusive criteria were: 1. HCC diagnosis according current guidelines, 2. never under surgical treatment, 3. Initially treated in out hospital and 4. survival patients with observation duration more than 5 years. A total 1834 patients met above criteria, and 1136 (61.9%) had short survival duration (<2 years), 451 (24.6%) had medium survival (2 to 5 years), and 247 (13.5%) had long survival (>5 years). All well-known prognostic factors were collected, such as age, gender, liver function reserve, tumor staging, alpha-fetoprotein (AFP) and et al. Besides, four interventional prognostic factors were also included, i.e. initial treatment modality, outcomes of 1st treatment, outcomes of 2nd treatment and anti-viral therapy to chronic hepatitis B or C. Propensity score matching was use for improvement of compatibility between medium and long survival groups. Binary logistic regression was used to calculate univariate and multivariate odds ratio (OR) and its 95% confidence interval (CI).

Results: The significant prognostic factors between these two groups were albumin, bilirubin, ascites, Child-Pugh classification, AFP levels, BCLC staging and all the 4 interventional factors. After propensity score matching to the well-known unmodifiable factors, 223 well-matched pairs were further analyzed. Multiple logistic regression showed that recurrence within one year after 1st treatment (OR: 2.17, 95% CI: 1.35~3.48), incomplete treatment of 2nd treatment (2.02, 1.28~3.19) and never treated by anti-viral agents (1.64, 1.07~2.50) were independent poor prognostic factors.

Conclusions: Interventional factors, such as complete treatment and anti-viral treatment, were independent prognostic factor of HCC patients underwent non-surgical treatment. Based on this study, we suggested that we should treat patients as complete as possible, we should detect recurrence tumor as early as possible to increase the chance of curative treatments and we should use anti-viral treatment for chronic hepatitis B or C if indicated.

P2-07

Prognosis of the Patients with Hepatocellular Carcinoma with Bile Duct Invasion

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Background: Hepatocellular carcinoma (HCC) with bile duct invasion is much rarer than vascular invasion, therefore, is not well characterized nor studied until these days. There is no globally standardized staging system for HCC, but it is known that bile duct invasion on pathologic finding itself is not the independent factor for expecting prognosis of HCC after operation. The purpose of this study is to present the characteristics of HCC with bile duct invasion and to compare the prognosis of that with other prognostic factors.

Methods: Between January 2009 and December 2011, 365 patients underwent hepatic resection at Seoul National University Hospital (SNUH) for HCC. We reviewed all patients' preoperative clinical information, epidemiologic and biochemical data, radiologic tumor size and numbers, operative findings, pathologic data such as tumor grade (TNM staging by AJCC), bile duct and vascular invasion, size and Edmondson grade were collected to compare the implications of factors for prognosis. We compared overall survival and recurrence free survival to evaluate the prognosis of bile duct invasion.

Results: Among 365 patients, 13 patients were improved to have bile duct invasion on pathologic and radiologic findings. 286 patients were recurred after operation on 3-5 year follow up, and 70 patients were expired. By comparing the characteristics of the groups with and without bile duct invasion The

median age, preoperative tumor size and T-stage had no significant differences. The group with bile duct invasion showed more vascular invasion (11 in 13 (84.6%), than without bile duct invasion group (40.2%). For prognosis, the patients with bile duct invasion showed poor prognosis than without invasion. In multivariate comparison with other prognostic factors, bile duct invasion improved not to have affect for the prognosis of HCC independently, but subgrouping by T-stage, the bile duct invasion was proved to be the independent factor for the prognosis of HCC in early stage (T1 and 2).

Conclusion: Bile duct invasion accompanies vascular invasion in most cases. Bile duct invasion itself is not the independent prognosis factor for HCC. But in early HCC (T1 and T2) with bile duct invasion has poor prognosis.

P2-08

HepPar-1 Loss and CK20 Expression Are Correlated with Poor Survival of Hepatocellular Carcinoma Patients

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Background: Hepatocellular carcinoma (HCC) is the 6th most commonly developed malignant neoplasm and the 2nd most common cause of cancer death. Cytokeratin 20 (CK20) is

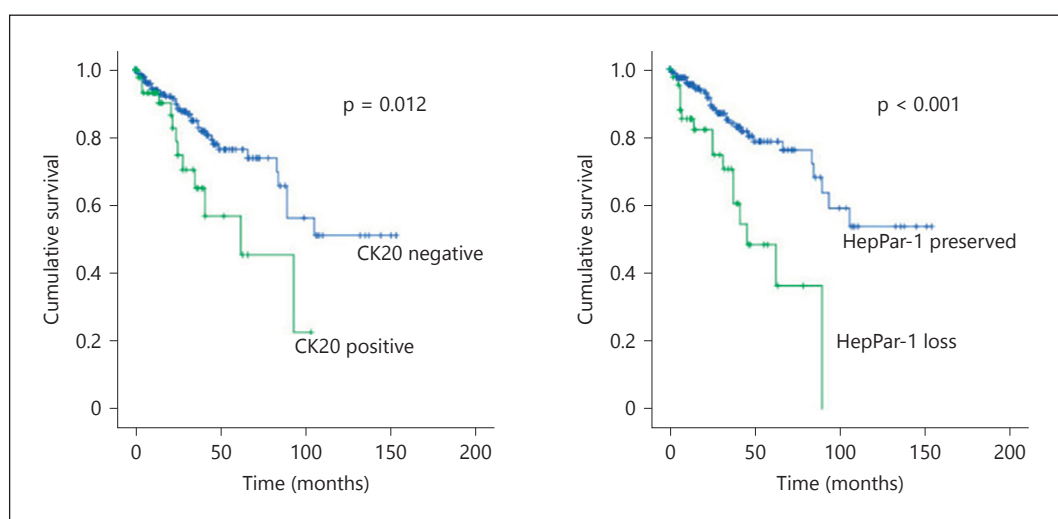


Fig. 1. Kaplan-Meier plots of overall survival (for Abstract P2-08).

commonly expressed in intestinal epithelium and known as useful marker for colorectal cancer. Cytokeratin 19 (CK19), usually expressed in embryonal hepatocytes and bile ducts, is commonly used as marker for stemness of HCC. Most HCCs are considered to show no expression of these markers. There are some reported cases of HCCs showing positive expression of these markers, but their significance are not fully established.

Design: Immunohistochemical expressions of CK20, CK19 and HepPar-1 were evaluated using 2-mm core tissue microarray from 294 patients with HCC.

Results: Positive expressions of CK20 and CK19 were seen in 50 (17%) and 29 (10%) of patients, respectively. Loss of expression of HepPar-1 was identified in 44 (15%) of patients. On univariate analysis, positive expression of CK20 ($P = 0.012$) and loss of expression of HepPar-1 ($P < 0.001$) were significantly associated with poor overall survival [Figure 1]. Positive expressions of CK20 and CK19, and loss of expression of HepPar-1 were correlated with higher Edmondson-Steiner's grade with statistical significance ($P = 0.014$, $P = 0.001$ and $P = 0.001$, respectively). On multivariate analysis, tumor stage, vascular invasion and loss of expression of HepPar-1 were independent prognostic factors significantly associated with overall survival ($P < 0.001$, $P = 0.009$ and $P = 0.001$, respectively).

Conclusion: CK20, CK19 and HepPar-1 can be used as markers for identifying differentiation of HCC. Positive expression of CK20 and loss of expression of HepPar-1 can be indicators for poor prognosis.

P2-09

Withdrawn

P2-10

Clinical Characteristics of Hepatocellular Carcinoma in Elderly Patients:

A Retrospective, Multicenter Study

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Background: The incidence of hepatocellular carcinoma (HCC) in elderly patients (ages sixty-five and older) in Japan has been on the increase, but the clinical characteristics of patients with HCC have not been well described. The aim of the present study was to evaluate the impact of aging on the clinical characteristics findings and the survival of HCC patients.

Method: A total of 2,370 patients with HCC diagnosed between 1999 and 2011, were recruited for this study. The

age of HCC was categorized to four groups; not old: sixty-four and younger, young old: sixty-five to seventy-four, old old: seventy-five to eighty-four, oldest old: eighty-five and older. The significance of clinical parameter was examined for elderly HCC patients using logistic regression analysis.

Result: Multivariate analysis identified sex (female, HR 2.20), body mass index (BMI) (≥ 25 , HR 0.35), alcohol consumption (not excessive drinker, HR 0.64; excessive drinker, HR 0.36), Child-Pugh grade (B, HR 0.68; C, HR 0.32), etiology of liver disease [hepatitis B infection (HBV), HR9.12; HBV and hepatitis C virus infection (HCV), HR4.32; non-hepatitis virus infection, HR11.28], alanine aminotransferase (ALT) (>46 IU/l, HR 0.53), α -fetoprotein (AFP) (≥ 200 ng/ml, HR 0.53) and Tumor-Node-Metastasis (TNM) stage (II, HR1.65), as independent and significant risk factors for elderly HCC patients. Additionally, the significant risk factors for elderly HCC patients according to four age groups are presented. The ratio of male, BMI, alcohol intake patients, ALT, and AFP decreased significantly from 80%, 23.0, 40%, 50 IU/ml and 48.7 ng/ml in not old group to 57%, 21.6, 26%, 28 IU/l and 12.8 ng/ml in oldest old group, respectively. The ratio of Child-Pugh grade A and non-hepatitis virus infection increased significantly from 60% and 17% in not old group to 80% and 43% in oldest old group, respectively. When patients were classified according to the TNM stage, patients in the oldest old group with TNM stage I or II had a lower cumulative survival rate than those in the younger three groups, whereas in TNM stage III or IV were not significant differences four groups.

Conclusion: Oldest old patients had more mild underlying liver damage. However, the survival outcome of oldest old patients was different from that of younger patients in TNM stage I or II. It appears that eighty-five years and older patients with HCC were poorer prognosis than that younger patients in early stage HCC.

P2-11

Changes of Liver Cirrhosis Incidence, Primary Liver Cancer Incidence and Primary Liver Cancer Mortality Rates in Republic of Korea

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Background/Aim: We aimed to explore recent 10 years (2004–2013) incidence trends of liver cirrhosis and primary liver cancer (subcategories: hepatocellular carcinoma, intra-hepatic bile duct and unspecified liver tumors) and mortality trend of primary liver cancer in Republic of Korea.

Methods: We analyzed trends of incidence rates (the number of patients divided by total population covered with health insurance service) per 100,000 people by age and sex for recent 10 years in liver cirrhosis and primary liver cancer from

data of National Health Insurance Service (NHIS). We also analyzed trends of primary liver cancer mortality rates per 100,000 people by sex for recent 10 years in primary liver cancer from data of Korean Statistical Information Service (KOSIS).

Results: During recent 10 years (2004–2013), liver cirrhosis incidence rates per 100,000 people decreased among men aged 20–69 years and women aged 20–59 years but increased in men aged ≥ 70 years and women aged ≥ 60 years. Primary liver cancer incidence rates per 100,000 people decreased among men aged 20–49 years and women aged 20–59 years but increased in men aged ≥ 50 years and women aged ≥ 60 years. All trends showed significant changes. The overall mortality rates of primary liver cancer decreased in both sexes but did not show statistically significant changes.

Conclusions: The number of patients with liver cirrhosis and primary liver cancer has increased in the last decade. However, the trend was different by age, and the growth rate was small or declined in the young. The mortality caused by primary liver cancer for the past 10 years has decreased. This will help to predict the prospect of liver cirrhosis and primary liver cancer in Republic of Korea.

P2-12

Hepatocellular carcinoma Detected by Regular Surveillance

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Introduction: Hepatocellular carcinoma (HCC) is the third most common cause of cancer death worldwide and is in second place in Taiwan. Current international guidelines recommend regular ultrasonography (US) surveillance in people with high risk in HCC development, followed by a recall procedure upon detection of any suspicious nodule. Besides, some patients having suspicious nodules are diagnosed during prolong follow-up since they are not readily diagnosed by the recall procedure. We aim to examine if prolong follow-up in this group has impacts on outcome.

Material and Method: This is a single center, retrospective cohort study. During 2010–2012, total 1419 patients were registered having HCC in our hospital database. 33 patients were excluded because of prior treatment or incomplete record. In all the reminder patients, we examined the dynamic images or US-guided biopsy and review the preceding US. The positive US is defined if the sonographic findings were consistent to the confirmation image. Surveillance is defined at least one US exam was done, during the one year before the most early positive US. Among the reminder patients, 198

patients were diagnosed during regular liver US surveillance (with 3, 6, or 12 $\pm$ 1 month interval), the other 1188 patients were assigned as non-surveillance group, and staging based on Barcelona-Clinic liver cancer (BCLC) system was evaluated. The surveillance group were subdivided into three groups: (A) immediate diagnosis: the diagnosis of HCC was made immediately by any recall procedure (image or biopsy) after suspicious US, (B) enhanced follow-up: initial recall procedures were negative or indecisive, and the diagnosis was made later by further workup during follow-up. (C) beyond US: the diagnosis of HCC were made purely by dynamic CT or MRI surveillance or any recall procedure triggered by elevation of alpha-fetoprotein (AFP), and the tumor had never been detected by prior US despite regular surveillance.

Result: In our study, the stage distributions were (n = 198, stage 0: 25.8%, stage A: 56.1%, stage B: 11.6%, stage C: 5.1%, stage D: 1.5%) in the surveillance group versus (n = 1188, stage 0: 8.6%, stage A: 28.6%, stage B: 22.6%, stage C: 33.2%, stage D: 7.6%) in the non-surveillance group. Significantly more early HCCs (BCLC stage 0-A) were diagnosed in the surveillance group compared to non-surveillance group. (83.1% vs. 36.6%, $p < 0.001$). Among the three surveillance subgroups, baseline characteristics were similar despite significant more patients in the group C (72%) versus group A (35.2%) and group B (20.9%) having higher rate of AFP elevation (>20 ng/ml) ($p < 0.001$). The BCLC stages upon diagnosis and annual survival rates did not differ among surveillance subgroups. Estimated follow-up time from positive US to confirmation of HCC in group B is 8 (2–67) months (median).

Conclusion: Stage shift was observed in HCC patients received regular US surveillance. Despite a certain time lag exists between positive US and diagnosis of HCC in patients with enhanced follow-up, their HCC stage and survival did not differ from the other surveillance groups, indicating the diagnostic criteria by international guidelines seems to be appropriate.

P2-13

Consideration of Albumin, Bilirubin and Hepatitis B Virus Viral Titer Improves Diagnostic Accuracy in Surveillance of Hepatitis B Virus Associated Hepatocellular Carcinoma

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Background: Chronic hepatitis B (CHB) is one of the most important risk factors of hepatocellular carcinoma (HCC). Therefore, periodic surveillance is required for CHB patients. Currently ultrasound exams and AFP tests are most widely used for HCC surveillance, but hepatitis B virus (HBV)

proliferation per se can increase AFP levels in CHB patients without HCC. Our previous study found that bilirubin, albumin and HBV DNA titer were significant determinants for AFP levels. This study tried to determine whether a corrected AFP test model considering these parameters have improved performance in the surveillance of HBV-associated HCC.

Methods: This study included 6913 patients with CHB infection who received HCC surveillance at Seoul National University Bundang Hospital between 2003 and 2015. We used modified UICC system as stage of HCC. Multiple linear regression was used to calculate coefficients for corrected AFP test models. ROC analysis was used to compare performance of AFP models for HCC surveillance.

Results: A total of 6564 non-HCC patients and 349 HCC patients were finally enrolled. Corrected AFP was calculated as follows: $\log \text{AFP} + 0.018 \times \text{bilirubin (mg/dl)} + 0.051 \times \log \text{HBV DNA (copies/ml)} - 0.103 \times \text{albumin (g/dl)}$. The area under the curve for HCC was 0.901 in AFP (95% CI, 0.893–0.908) and 0.912 in corrected AFP (95% CI, 0.905–0.919) ($p = 0.0047$).

Conclusions: Corrected AFP considering bilirubin, albumin and HBV DNA levels showed better performance compared to AFP alone for the surveillance of HBV associated HCC.

P2-14

Effect of Hepatitis B Virus Viral Load on the Performance of Alpha-Fetoprotein During Surveillance of Hepatocellular Carcinoma

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Background: Alpha-fetoprotein (AFP) is a marker that is commonly used in hepatocellular carcinoma (HCC) surveillance. However, chronic hepatitis B virus (HBV) infections elevate AFP levels, which increases the chances of obtaining false-positive results. The aim of this study is to assess the effect of the HBV viral load on the AFP performance as a biomarker in the surveillance of HCC.

Methods: For this retrospective cohort study, we examined consecutive HBV-associated liver cirrhosis patients who underwent more than 6 months of surveillance for HCC between May 2003 and December 2010. Diagnosis of liver cirrhosis was based on clinical, laboratory and imaging findings. Surveillance program was comprised of periodic ultrasound exams and AFP tests every 3–6 months. Diagnosis of HCC was based on two or more contrast-enhanced imaging studies. The diagnostic performance of AFP was compared by measuring area under the curve (AUC) of receiver operating characteristics analysis.

Results: A total of 624 HBV-associated liver cirrhosis patients were enrolled in this study. The median duration of

follow-up was 67 months. The incidences of HCC were 2.4%, 10.6%, 17.6% in 1-, 3-, 5-years respectively. Among these patients, maximum HBV viral loads were less than 10^5 copies/ml in 501 patients, while the remaining 123 patients had maximum viral loads greater than 10^5 copies/ml. The incidence of HCC was significantly higher in the high maximum HBV DNA group (19.5% vs. 9.5%, $p < 0.01$). The initial and final AFP values were significantly higher in the high maximum HBV DNA group. The AUC value was also greater in the high maximum HBV DNA group compared to low maximum HBV DNA group (0.771, 95% CI 0.761–0.780 vs. 0.538, 95% CI 0.514–0.562).

Conclusions: Results of this study show that the diagnostic value of AFP was lowered in patients with lower HBV viral loads.

P2-15

Long-Term Effect of Sustained Virologic Response on Prevention of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C

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Background/Aims: Oral direct acting antiviral (DAA) agent is expensive to be used routinely and not yet available for clinical use in Korea. So, Peginterferon and ribavirin therapy is still a standard treatment option in Korea. The long-term effect of sustained virologic response (SVR) according to fibrosis stage on prevention of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C is unclear. In this study, we investigated the influence of peginterferon and ribavirin therapy on the risk of HCC in Korean CHC patients, especially in relation to the stage of liver fibrosis.

Patients and Methods: A total of 304 CHC patients treated with peginterferon/ribavirin were observed with a median follow-up duration of 54 months (range, 4 to 118 months). The incidence and relevant risk factors for development of HCC were analyzed.

Result: By intention to treat analysis, overall SVR rates in genotype 1 patients and genotype non-1 patients were 57.2% (87/152) and 86.2% (131/152). The incidence rates per 10000 person-years of HCC were 80 for SVR and 360 for non-SVR patients. According to fibrosis stage, the incidence rate of HCC were 0 for F0–2, 503 for F3, 1093 for F4. In multivariate analysis, liver cirrhosis (HR: 10.9, 95% CI: 3.6–33.1; $P < 0.001$) and SVR status (HR: 0.37, 95% CI: 0.15–0.91; $P = 0.032$) were independent predictors of HCC. The cumulative incidence of HCC was significantly lower in SVR patients than in

non-SVR patients, and in F0-2 patients than in F3 patients. ($P = 0.048$, $P < 0.001$, by log-rank test).

Conclusion: In Korean patients with CHC, achievement of a SVR after peginterferon/ribavirin therapy was associated with a reduction of HCC development. Irrespective of SVR status, however, patients should undergo surveillance for HCC, especially in patients with advanced fibrosis.

P2-16

Risk Factors of Cryptogenic Hepatocellular Carcinoma in Patients with Low Body Mass Index or No Metabolic Syndrome

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Aims: Metabolic syndrome (MS) is emerging as a major cause of cryptogenic hepatocellular carcinoma (HCC), but many patients have been diagnosed with cryptogenic HCC without MS. We investigated risk factors for cryptogenic HCC in patients with low body mass index (BMI) or no MS.

Methods: 36 patients were diagnosed with HCC, not associated with hepatitis B, hepatitis C, or alcohol intake, over 10 years at a university referral hospital. These patients' clinical data were analyzed retrospectively including BMI score and risk factors for MS. Patients with fewer than two risk factors for MS ($n = 16$) were compared with patients with more than one risk factor ($n = 20$). Patients with high BMI (≥ 23 kg/m², $n = 20$) were also compared with patients with lower BMI ($n = 16$).

Results: Patients with fewer than two risk factors for MS were significantly associated with smoking, and the presence of HBs antibodies versus patients with more than one risk factors (50.5% vs. 15%, respectively; $p = 0.034$ and 58.3% vs. 21%, respectively; $p = 0.026$). But, only smoking was statistically significant on multivariate analysis. Patients with lower BMI were significantly associated with the presence of HBs antibodies versus patients with high BMI (69.2% vs. 11.1%, respectively; $p = 0.003$). Although this association was not statistically significant on multivariate analysis. Peaks of BMI were observed in two regions (18.5–22.9 and 25–29.9 kg/m²). But, there were no difference in clinical data.

Conclusions: Smoking is a potential risk factor for cryptogenic HCC in patients without MS. Remote HBV infection is a potential risk factor for cryptogenic HCC in patients without MS or with low BMI.

P2-17

Pathological Diagnosis and the Problems of the Benign Hepatocellular Nodular Lesions – Focal Nodular Hyperplasia, Hepatocellular Adenoma and Borderline Lesion –

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Background: Benign hepatocellular nodular lesions (BHNs) includes focal nodular hyperplasia (FNH), hepatocellular adenoma (HCA), nodular regenerative hyperplasia (NRH), and other nodular lesions. These lesions are diagnosed based on detailed clinical and histopathological analyses. The 2010 World Health Organization classification (WHO) grouped HCA into four subtypes according to the molecular pathology, based on the results of immunohistochemical staining. Immunohistochemical staining for glutamine synthase (GS) is shown to be useful in differentiating between HCA and FNH. HCA is classified into four subtypes, namely inflammatory HCA (I-HCA), HNF1-alpha-inactivated HCA (H-HCA), beta-catenin-activated HCA (b-HCA), and unclassified HCA (U-HCA), based on the results of immunostaining for serum amyloid A (SAA), C-reactive protein (CRP), liver type fatty acid binding protein (L-FABP), and beta-catenin. Each individual subtypes displays some unique characteristics. An important observation is that the transformation rate of b-HCA is higher than that of the other subtypes. In this study, these disease factors and characteristics were examined in Japanese patients.

Methods: Seventy cases (113 nodules) of BHNs were examined in our hospital, and other affiliated hospitals, and from among consultation cases. The samples were immunostained for glutamine GS, SAA, CRP, L-FABP, beta-catenin, organic anion transporting polypeptide 1B3 (OATP1B3), glypican 3 (GPC3), heat shock protein 70 (HSP70), and cytokeratin 7 (CK7).

Results: When stained for GS, majority of the FNH nodules showed a map-like pattern, while most of the HCA nodules displayed a diffuse pattern. The rates of occurrence of I-HCA, H-HCA, b-HCA, and U-HCA were similar to those described in the WHO classification. However, some cases showed atypical positive immunohistochemical staining patterns for GS and SAA. Some nodules displayed typical characteristics of FNH on macroscopic examination and hematoxylin and eosin staining; however, these nodules showed HCA-like staining patterns on immunohistochemical

staining. A few cases also showed the coexistence of HCA with FNH.

Conclusions: The results suggest the reliability of this classification and diagnostic procedure in Japanese BNL patients.

The nodules that showed atypical positive immunostaining for GS and SAA, may indicate the transformation of lesions from the FNH to HCA types. Macroscopic analysis and hematoxylin and eosin staining of these nodules presented a diagnosis of FNH; the accurate diagnosis of HCA was obtained only by immunostaining. Therefore, immunohistochemistry must be a mandatory diagnostic procedure for the identification and classification of BNLs. These results reveal the need for revision of conceptions, definitions, and diagnosis of nodular lesions such as FNH. The diagnostic procedures, used in this study could help in interpreting, and avoiding these issues.

P2-18

Peptidomics Analysis of Serum Reveals Circulating Cell-Derived Peptides as Novel Biomarkers for Chronic Hepatitis and Hepatocellular Carcinoma

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Although circulating peptides in blood may serve as surrogate markers for disease, there is no convincing report of valuable low abundance peptides of cellular origin identified as potential biomarkers because they are masked by high abundant plasma proteins. The outcome of patients of hepatocellular carcinoma (HCC) remains poor because of inaccuracy of known tumor markers in early stage-HCC and also few markers for chronic hepatitis (CH) and liver cirrhosis (LC). We established a quantitative peptidomic methodology using MS to screen for masked peptide biomarkers in circulating blood and comprehensively analyzed 181 serum samples of liver disease and HCC. By efficient peptide extraction by acid-boiling and extensive fractionation using two-dimensional microflow HPLC combined with MALDI-TOF MS/MS, we identified twelve cell-derived peptides associated with cancer and a glycosylated peptide with high sensitivity and specificity for the diagnosis of HCC and CH, respectively. These biomarkers were verified by LC-ESI-TOF MS/MS or immunoprecipitation-MS with stable isotope-labeled peptides as internal standards. Serum NPY1R peptide levels showed significantly up-regulated in HCC and, in comparison between normal and HCC, the area under the receiver-operating char-

acteristic (ROC) curve (AUC) was 0.99 ($p = 0.0001$). Its AUC value was 0.76 ($p = 0.0001$) in CH and LC versus (vs.) HCC. Peptide biomarkers including NPY1R showed more than 70% sensitivity in HCC which were negative for conventional tumor markers, and combination of two or three of them showed higher AUC (0.82 or 0.85) than a fetoprotein (AUC = 0.75). Glycosylated ITIH4 peptide showed remarkable diagnostic potential in the CH vs. normal comparison (AUC = 0.88). Finally, for clinical use, we developed rapid LC-ESI-TOF MS and LC-ESI-multiple reaction monitoring-MS assays using ultra-fast liquid chromatography enabled us to quantify the biomarker within a few min. These results indicate peptides circulating in blood, particularly those of cellular origin, are potentially valuable biomarkers that could impact early diagnostics and therapeutic intervention in cases of chronic liver disease.

P2-19

Adjusting the Fibrotic Burden Using Transient Elastography Reveals Similar Longterm Outcomes in Chronic Hepatitis B Patients Treated with Lamivudine or Entecavir: A Propensity-Score Matched Analysis

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Backgrounds: Entecavir is thought to be associated with a significantly lower risk of liver-related death or transplantation compared with lamivudine, despite their similar influences on the risk of developing hepatocellular carcinoma (HCC) among patients with chronic hepatitis B (CHB). This study investigated whether this difference in the long-term outcomes of lamivudine and entecavir remains after adjusting for the background fibrotic burden, based on liver stiffness values determined using transient elastography (TE), which can accurately assess the degree of liver fibrosis.

Methods: Patients with CHB treated with lamivudine ($n = 425$) or entecavir ($n = 644$) as the first-line therapy between 2005 and 2013 were considered eligible. Patients with an alanine aminotransferase [ALT] >300 IU/L were excluded. Patients treated with lamivudine were matched to those treated with entecavir using a propensity-score matched (PSM) model in a 1:1 ratio, using five variables (PSM model 1: age, gender, HBeAg, ALT, and liver stiffness [LS]) and six variables (PSM model 2: the five variables in PSM model 1 plus ultrasonographic cirrhosis). The time to the development of HCC or liver-related events (LREs) including HCC, hepatic decompensation, or liver-related death was assessed using the method of Klein and Moeschberger.

Results: During the follow-up (median 49.5 [interquartile range, 31.4–86.6] months), 91 (8.4%) and 104 (9.4%) patients experienced HCC and LRE, respectively. The LS value was an independent predictor of HCC and LREs (all $P < 0.05$), along with age, gender, and platelet count, whereas entecavir use and rescue therapy were not significant for predicting HCC and LRE development, even in univariate analysis (all $P > 0.05$). We matched all cases treated with lamivudine to non-cases treated with entecavir, resulting in propensity-matched sets with the same sample size ($n = 764$, 382 patients each for lamivudine and entecavir) using PSM models 1 and 2. With PSM model 1, patients treated with lamivudine had a similar cumulative incidence of HCC (1.7 vs. 1.9/100 person-years) or LRE (2.1 vs. 2.0/100 person-years) compared to non-cases with entecavir (all $P > 0.05$). Likewise, with PSM model 2, patients treated with lamivudine had a similar cumulative incidence of HCC (1.8 vs. 1.8/100 person-years) or LRE (2.1 vs. 1.8/100 person-years) compared with non-cases (all $P > 0.05$). Additionally, when the entire population was divided into sub-cohorts with LS value ≤ 13 kPa and > 13 kPa, the known cutoff value for diagnosing cirrhosis, and patients treated with lamivudine were matched to those treated with entecavir using PSM models 1 and 2, the cumulative incidence of HCC and LRE did not differ in either the sub-cohort with LS value ≤ 13 kPa (0.7 vs. 0.9/100 person-years for HCC, 1.5 vs. 0.9/100 person-years for LRE using PSM model 1; 1.3 vs. 1.2/100 person-years for HCC, 1.5 vs. 1.2/100 person-years for LRE using PSM model 2) or the sub-cohort with LS value > 13 kPa (3.3 vs. 3.8/100 person-years for HCC, 4.0 vs. 4.4/100 person-years for LRE using PSM model 1; 3.1 vs. 3.4/100 person-years for HCC, 3.9 vs. 4.1/100 person-years for LRE using PSM model 2) (all $P > 0.05$).

Conclusions: The background fibrotic burden, not the type of antiviral agent, independently influenced the risks of developing HCC or LRE, given that timely rescue antiviral therapy is available. Therefore, the degree of liver fibrosis should be assessed accurately for effective surveillance strategy.

P2-20

Noninvasive Diagnosis of Malignant Liver Tumors Using Shear Wave Ultrasound Elastography

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Background and Aim: In recent years, the evaluation of liver fibrosis using ultrasound elastography to estimate liver stiffness has become an important alternative to liver biopsy. Our institution was an early adopter of shear wave ultrasound elastography, a widely-used, noninvasive method of assessing liver fibrosis. In addition to liver fibrosis, we also have been using shear wave ultrasound elastography for differentiating between various malignancy liver tumors. In this study, we assessed the utility of shear wave ultrasound elastography in differentiating between malignant liver tumors (hepatocellular carcinoma, HCC; metastatic liver cancer, MET's; intrahepatic cholangiocarcinoma, ICC; and cholangiolocellular carcinoma, CoCC).

Methods: We evaluated 180 cases (male, 128; female, 52; average age, 68.2 ± 9.67 ; HCC, 114; MET's, 55; ICC 9; CoCC, 3) diagnosed by imaging or histological studies at our institution from October 2008 to February 2015. Shear wave ultrasound elastography was performed using Virtual Touch Quantification (VTQ) by Siemens ACUSON S2000/S3000. Shear wave velocities (Vs. value m/s) were measured 3 to 5 times at a similar depth ROI for tumoral and nontumoral regions with mean values recorded. This study was approved by the hospital ethics committee at our institution.

Results: Tumor diameters (mm, mean $\pm$ SD) were as follows: HCC, 35.7 ± 25.4 ; MET's, 27.9 ± 15.2 ; ICC, 44.9 ± 25 ; and CoCC, 51.3 ± 40 . Vs. values from B-mode findings were as follows: hyperechoic HCC, 1.64 ± 0.44 ; hypoechoic HCC, 1.53 ± 0.78 ; and mosaic HCC, 1.79 ± 0.66 . Regarding the degree of tumoral differentiation, well-differentiated HCC was 1.52 ± 0.44 , moderately differentiated was 1.75 ± 0.71 , and poorly differentiated was 2.00 ± 1.28 . Vs. values from B-mode findings with or without marginal low area of HCC is 1.69 ± 0.56 and 1.73 ± 0.83 respectively. No significant difference in Vs. values,

an indicator of tumoral density, were observed in any cases. Tumoral and nontumoral Vs. values according to tumor type were as follows: HCC, 1.71 ± 0.68 and 1.89 ± 0.72 ; MET's, 2.69 ± 1.10 and 1.24 ± 1.24 ; ICC, 2.58 ± 0.55 and 1.55 ± 1.55 ; CoCC, 3.03 ± 0.36 and 2.15 ± 2.15 . These data which demonstrate Vs. values for HCC were significantly lower than those for other malignancies (MET's, ICC, CoCC: non-HCC, ($P < 0.001$). In cases of MET's and ICC, tumoral Vs. values were greater than nontumoral Vs. values ($P < 0.01$). In particular, in hypoechoic lesions, MET's Vs. values were significantly higher than that for HCC ($P = 0.0029$), with no significant difference observed between non-HCC. In the primary sites of MET's, to investigate stomach, pancreas, and large intestine, Vs. values were determined as 2.91 ± 1.15 , 1.86 ± 0.94 and 2.49 ± 0.72 respectively. No significant difference was observed in Vs. values according to primary tumor sites.

Conclusion: The measurement of Vs. values of malignant liver tumor using shear wave ultrasound elastography may be useful in the noninvasive differential diagnosis of HCC and non-HCC.

P2-21

Magnetic Resonance Elastography (MRE) in Assessing Hepatic Fibrosis: Comparative Study with Transient Elastography (TE) in Same Patients with Histological Data

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Background: Regardless of etiology, chronic liver diseases (CLD) can be associated with liver fibrosis, which result in complicating a hepatocellular carcinoma or varices. Monitoring a progression of fibrosis is important to manage patients with CLD. The current diagnostic gold standard to diagnose advanced fibrosis is liver biopsy, although it has potential complications and difficulty of repeat examination. Recently, some non-invasive methods such as ultrasound elastography or MR elastography are emerging and literatures about them have been published. Now, we also evaluate quantitative measurement of liver stiffness and investigate the diagnostic performance of MRE and ultrasound-based transient elastography in our hospital.

Material and Methods: Retrospective study was approved by institutional review board. Between October 2013 and January 2015, 116 patients with chronic liver disease underwent MRE to measure liver stiffness (LS) (kilopascals; kPa). Of the 116 patients, 40 patients also underwent both TE and liver biopsy, and the interval between the liver biopsy and the both MRE and TE was less than 90 days. MRE

were performed with 1.5T scanner and TE with FibroScan system (Echosens, Paris, France). LS values on MRE were measured on the anterior segment of the right lobe. Histological fibrosis grade (F0-4) and each of the MRE and TE parameters were correlated by using Spearman's correlation. Steel-Dwass test was used for multiple comparisons for histological assessment. The overall predictive ability of MRE and TE in assessment of fibrosis was compared by constructing a receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was calculated and Delong's test on the basis of histopathologic analysis was performed.

Results: MRE showed the higher correlation coefficient ($r = 0.82$) compared with TE (0.72). Both MRE and TE could show a significant difference for F1 vs. F3, F1 vs. F4, F2 vs. F3 and F2 vs. F4 ($P < 0.05$ for all). In ROC analysis, MRE showed the higher AUC than TE: the optimal cutoff MRE LS values for $\geq F2$ and $\geq F3$ were 3.92 kPa (AUC 0.88, sensitivity 79%, specificity 81%) and 4.97 kPa (AUC = 0.96, sensitivity 92%, specificity 89%), respectively. For detection of each $\geq F2$ and $\geq F3$, AUC for MRE was higher than for TE though not significant (0.88 vs. 0.79, $P = 0.13$; 0.96 vs. 0.96, $P = 1.0$, respectively).

Conclusion: Both MRE and ultrasound-based TE can assess hepatic fibrosis. Both have comparable accuracy for detecting liver fibrosis in chronic liver disease. They are non-invasive and useful applications for evaluating the degree of hepatic fibrosis especially in detection of extensive fibrosis ($\geq F3$). The individual techniques reliably detect or exclude extensive liver fibrosis in 90%.

Acknowledgement: We would like to express the deepest appreciation to Dr. Yada who provided valuable ultrasound-based TE data.

P2-22

VF Map Scores (Virtual Touch Quantification, Fasting Plasma Glucose, Male, Age, Platelets) for Prediction of Hepato-Carcinogenesis

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Background and Aims: Shear wave elastography is an easily measureable test in daily clinical practice, since it is non-invasive and a good indicator of liver fibrosis. The aim for

this study is to reveal the risk of liver carcinogenesis using Virtual Touch Quantification (VTQ).

Methods: Our research model was a retrospective cohort study. We continued to follow up 1847 patients for 40.5 ± 16.4 months: 73 patients developed hepatocellular carcinoma (HCC), the other 1774 patients did never develop HCC. We examined carcinogenesis factors by cox regression analysis.

Results: The univariate analysis between two groups: there were significant difference in age, sex, HCV infection, platelets, FIB4 index, VTQ, serum albumin and fasting plasma glucose (FPG) ($p < 0.05$). Cox regression analysis: there were significant differences in age, sex, platelets, FPG and VTQ ($p < 0.05$). Hazard ratio (HR) was 4.2 times in $VTQ \geq 1.35$ m/s, HR 2.2 times in $FPG > 100$ mg/dl, HR 2.1 times in male sex, HR 3.5 times in older than 61 y.o., HR 2.3 times in platelets $\leq 15.3 \times 10000/\mu l$. We suggest the scoring system which named 'VF map' scores (0–7 scores) according to this hazard ratio, in which we score 2 points for VTQ and Age, one point for FPG, Male and Platelets. 0–1 point patients never developed HCC. The carcinogenic rate of patients with 3–4 points of VF map score was around 5%, and with above 5 points of the score, liver carcinogenesis rate was more than 10–23%.

Conclusion: The VF map scores, which combines VTQ, FPG, Male, Age and Platelet counts, were very useful for predicting the HCC high-risk group.

P2-23

Sorafenib Might Inhibit Liver Fibrogenesis and Arterialization in Patients with Cirrhosis and Advanced Hepatocellular Carcinoma

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Background: It was reported that sorafenib (SF) might improve liver fibrosis and portal hypertension in an animal model.

Aim: The aim of this study was to clarify the effects of SF on hepatic function and liver fibrosis in patients with liver cirrhosis (LC) and advanced hepatocellular carcinoma (aHCC).

Patients/Methods: Sixty-two adult Japanese patients with LC and aHCC were treated with SF (400–800 mg/day for 4 weeks) between 2009 and 2013 at our hospital. Blood samples were collected in the early morning before and after

treatment to measure the serum concentration of the 7S domain of type IV collagen (type IV collagen) and the serum level of hyaluronic acid (HA). Liver fibrosis was assessed by virtual touch tissue quantification (VTTQ). Patients were underwent contrast enhanced ultrasonography (CEUS) using sonazoid before and after treatment of SF. The parenchymal blood flow (% of arterialization) were measured by using of arrival-time parametric imaging.

Results: Sixty-eight patients were in Child-Pugh class A and 21 patients were in class B. Eighteen patients had HBV-related LC, 47 patients had HCV-related LC, and 24 patients had non-B, non-C LC. There were 2 patients with stage III disease, 70 patients with stage IVA disease, and 17 patients with stage IVB disease. Assessment of liver damage showed that serum albumin was significantly lower after treatment compared with before treatment, although there were no significant differences of serum total bilirubin and % prothrombin after treatment. These changes led to an increase of the Child-Pugh score. Assessment of liver fibrosis showed that serum type IV collagen and serum P-III-P decreased significantly after treatment compared with before treatment, but there was no significant change of serum HA after treatment. The medium VTTQ value also decreased significantly after treatment compared with before treatment by decreasing of % of arterialization.

Conclusion: In patients with LC and aHCC, SF might inhibit liver fibrogenesis and arterialization, but it might also exacerbate liver damage as indicated by a decrease serum albumin.

P2-24

Withdrawn

P2-25

An Accurate Prognostic Staging System for Hepatocellular Carcinoma Patients After Hepatectomy

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Background: Hepatectomy is a good option for radical treatment of hepatocellular carcinoma (HCC) and prognosis of surgical cases correlates with several tumor factors and liver function. The aim of this study was to develop a simple and accurate predictive system for prognosis of HCC patients after surgery.

Table 1. PS score (for Abstract P2-25)

	Score		
	0	1	2
N x S factor	<4	4–9	>9
Liver Damage	A	B	

N x S = number and size; PS = predictive staging.
PS score = N x S factor score + Liver damage score.

Methods: On the basis of the cumulated data about clinicopathological features of 234 HCC patients following curative hepatectomy, we found that the mathematical product of tumor number and size (cm) (N x S factor) had high accuracy in predicting recurrence of HCC, and we established a simple predictive staging system (PS score) scored by the N x S factor and degree of Liver Damage classification proposed by the Liver Cancer Study Group of Japan (LCSGJ) as liver function. According these findings, we compared the availability of the PS score (score 0 to score 3) with those of six well-known clinical staging systems; TNM staging system (LCSGJ), TNM staging system (UICC), Japan Integrated Staging (JIS) score, modified JIS score, the Cancer of the Liver Italian Program (CLIP) score, and Tokyo score.

Results: The significant differences ($P < 0.05$) were shown in both disease-free survival (DFS) and overall survival (OS) between patients with different PS scores (PS score 0 vs. PS score 1; PS score 1 vs. PS score 2). There was a significant difference in DFS, but not OS, between patients with PS score 2 and those with PS score 3. The PS score had smaller values of the Akaike information criterion for both DFS and OS than any of the six well-known clinical staging systems.

Conclusion: These results suggest that the PS score is considered as a simple, accurate predictor for the prognosis of HCC patients after hepatectomy. Furthermore, this score is an easy-to-use preoperative assessment tool because the information on pathological vessel involvement is not needed, which is one of the parameters for the conventional TNM staging systems.

P2-26**Optimal Staging of Single Large Hepatocellular Carcinoma**

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Background: Although the Barcelona Liver Cancer Clinic (BCLC) staging system properly classifies patients and provides survival predictions and treatment options, the staging of single large hepatocellular carcinomas (SLHCCs), which defined as a single nodule >5 cm, is still controversial. This study was performed to determine the appropriate staging for SLHCCs.

Methods: Patients with newly diagnosed HCCs (BCLC stages A or B) were classified according to tumor burden: group 1, a single nodule >2 cm and ≤5 cm or 2–3 nodules ≤3 cm; group 2, a single nodule >5 cm; and group 3, 2 or 3 nodules >3 cm or >3 nodules. Survival analysis was performed according to tumor stage, type of treatment, and Child-Pugh grade.

Results: A total of 1,005 patients were enrolled. The mean age was 59.3 ± 10.6 years and 788 patients (78.4%) were men. Groups 1, 2, and 3 consisted of 613 (61.0%), 124 (12.3%), and 268 (26.7%) patients, respectively. The patients were treated with resection (202, 20.1%), radiofrequency ablation ± transarterial chemoembolization (RFA ± TACE; 311, 30.9%), and TACE (492, 49.0%). The survival of patients differed significantly according to tumor stage (median survival times were 75.2, 44.9, and 30.3 months in groups 1, 2, and 3, respectively; $P < 0.001$). In a multivariate analysis, group 2 had significantly worse survival than group 1 and similar survival to group 3.

Conclusions: Patients with SLHCCs had a worse prognosis than those in group 1 and a similar prognosis to those in group 3. Our results suggest that SLHCCs is best staged as BCLC stage B rather than BCLC stage A.

P2-27

The Direct Comparison Between Hong Kong Liver Cancer Classification and Barcelona Clinic Liver Cancer Classification for Prediction of Survival in Hepatocellular Carcinoma Patients

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Background: Although Barcelona clinic liver cancer (BCLC) classification has been used as staging system for hepatocellular carcinoma (HCC), various algorithms and staging systems were developed in many organizations. Recently, the Hong Kong Liver Cancer (HKLC) classification were proposed and the authors suggested it provide better prognostic classification than BCLC system. We verified the HKLC system and compared it with BCLC system for prediction of survival in HCC patients.

Methods: From 2004 to 2009, the medical records of 2293 HCC patients were retrospectively reviewed. Performance status, Child-Pugh score, tumor characteristics, treatment modality and survival were collected. Each patients were classified following both of HKLC and BCLC staging.

Results: Chronic hepatitis B (69.1%) was main attributable factor in development of HCC, followed by chronic hepatitis C (12.0%) and alcohol consumption (10.4%). Fifty percent of patients died during study period and median overall survival (OS) was 15 (0–181) months. The median overall survival was 39, 25, 21, 10.5, 6, 4, 2, 9, and 1 months in HKLC stage I, IIa, IIb, IIIa, IIIb, IVa, IVb, Va and Vb, respectively. Both HKLC and BCLC well differentiated the survival ($p < 0.001$). However, HKLC significantly well predicted 1 and 2 year of survival than BCLC (AUROC; 0.817 vs. 0.793, $p = 0.0002$; 0.806 versus 0.78 in 2 year, $p = 0.0001$). In the patients in BCLC B and HKLC II, the curative therapy group recommended by HKLC showed better survival compared to TACE which recommended by BCLC (69 vs. 29 months, $p = 0.002$). In BCLC B, the patients who treated according to HKLC showed better survival than who treated by BCLC (54 vs. 28 months, $p < 0.001$). In the patients in BCLC C and HKLC II, the curative therapy group recommended by HKLC showed better survival compared to systemic therapy which recommended by BCLC (28 vs. 4 months, $p < 0.001$). In BCLC C and HKLC III, the TACE group recommended by HKLC showed better survival compared to systemic chemotherapy which recommended by BCLC (8 vs. 4 months, $p = 0.026$). In BCLC C, the patients who treated according to HKLC showed better survival than who treated by BCLC (6 vs. 3 months, $p < 0.001$).

Conclusions: In our population, the HKLC system showed better survival compared to BCLC system. The more individualized therapy could be considered by HKLC for management of HCC patients resulting in improvement of prognosis.

P2-28

Selection Criteria for Hepatic Resection to Hepatocellular Carcinoma with Multiple Nodules at Intermediate Stage of BCLC

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Background: The Barcelona Clinic Liver Cancer (BCLC) classification recommends transarterial chemoembolization (TACE) for multinodular hepatocellular carcinoma (HCC). However, several reports suggested that hepatic resection to patients with multinodular or large hepatocellular carcinoma (HCC) provided better survival benefit than TACE. Almost all reports about the hepatic resection to HCC at the intermediate stage of BCLC (BCLC-B) were retrospective studies and the surgical indications for multiple tumors at BCLC-B have not been established. This study aims to clarify the survival benefit of hepatic resection for multinodular HCC at BCLC-B.

Methods: We retrospectively analyzed 85 patients with BCLC-B HCC who underwent liver resection in our institute. We divided these patients to three types based on radiological findings of tumor number and maximum tumor size in diameter. TYPE-1 was HCC with up to 3 lesions and < 5 cm in diameter. TYPE-2 is the case which is recommended to perform preoperative TACE and has up to 3 lesion/ > 5 cm or 4 nodules/any tumor size. TYPE-3 is the case which doesn't have indication of surgery at diagnosis. We evaluated the clinicopathological factors and survival according to this sub-classification.

Results: Median age was 65 years (range: 45 to 84 years) and there were 67 men and 18 women. 17 patients were positive of Hepatitis B surface antigen (HBs-Ag). 43 patients had the antibody for HCV (HCV-Ab). 43 patients (50.6%) were diagnosed as liver cirrhosis. Mean tumor size was 5.7 ± 2.2 cm in diameter. All patients had multiple tumors without macroscopic vascular invasion. 77 patients underwent curative surgery without macroscopic residual tumor (R0/1) and 8 patients underwent palliative surgery with residual tumor (R2). According to our sub-classification based on tumor size and number, 34 patients were classified as TYPE-1, 32 patients as TYPE-2 and 19 patients as TYPE-3. The 1-, 3- and 5-year overall survival rate of all 85 patients who underwent hepatic

resection were 85.5%, 76.0% and 63.4%, respectively. The 1-, 3- and 5-year overall survival rate of patients in TYPE-1 were 97.1%, 87.4% and 75.2%, those in TYPE-2 were 84.0%, 74.0% and 63.0%, those in TYPE-3 were 64.9%, 55.7% and 37.1%, respectively. Overall survival of patients in TYPE-1 was significantly better than that in TYPE-3. The prognosis of patients in TYPE-2 was worse than that in TYPE-1 and better than that in TYPE-3. However, the difference was marginally significant ($p < 0.1$). Univariate and multivariate analysis showed tumor size (less than 7 cm vs. 7 cm and over) and tumor number (up to 4 lesions vs. 5 lesions or over) were identified as independent prognostic factors for overall survival.

Conclusions: The results suggests that hepatectomy could be considered as a curative treatment for multinodular BCLC-B HCC. Our sub-classification can apply to select the initial treatment and make decision for surgery to BCLC-B HCC with multiple nodules.

P2-29

Utility of the Combination of Gray-Scale US and Perflubutane CEUS for Diagnosing the Early HCC: Comparison of Distinctly Nodular Type Well-Differentiated HCC

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Objective: To clarify the diagnostic value of combination of gray-scale and contrast-enhanced ultrasonography (CEUS) with perflubutane in determining the early hepatocellular carcinoma (HCC).

Methods: A total of 57 surgically resected well-differentiated HCCs with a maximum diameter of 5 cm or less were analyzed. HCCs were evaluated preoperatively using gray-scale and CEUS. HCCs were macroscopically diagnosed as vaguely nodular type or distinctly nodular type, which was defined as early HCC (e-HCC) and progressed HCC (p-HCC), respectively. Gray-scale US findings were evaluated as shape (round, roundish, or irregular), border (well-defined or poorly-defined), and intra-tumor (hyper, hypo, iso, heterogeneous, or mosaic). CEUS findings were evaluated during the arterial phase (vascularity [finely homogeneous, dendritic, or chaotic] and enhancement of perfusion [homogeneous or heterogeneous]), portal phase (presence or absence of washout), and post-vascular phase (echo intensity level [defect, incomplete defect, or iso]).

Results: Seventeen HCCs were categorized as e-HCCs and the remaining 40 were categorized as p-HCCs. Receiver operating characteristic (ROC) curve analysis for the diagnosis of e-HCC yielded area under the ROC curve (A_z) values for border in the gray-scale US and echo intensity level in the CEUS post-vascular phase of 0.803 and 0.807, corresponding to moderate diagnostic value, respectively. Multiple logistic regression analysis also indicated that both of gray-scale US and CEUS findings were independently associated with e-HCC. The A_z value for the combination of border and echo intensity for the diagnosis of e-HCC was 0.902 (95% CI, 0.780–0.959), corresponding to high diagnostic value.

Conclusion: Combination of gray-scale US and CEUS can provide high quality imaging assessment for determining the e-HCC.

P2-30

Differential Diagnosis of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Contrast-Enhanced Ultrasound

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Background: The ability of contrast-enhanced ultrasound (CEUS) in differential diagnosis between hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) is still controversial.

Methods: We reviewed CEUS imaging of 819 patients (HCC = 546, ICC = 273) with a pathological diagnosis. The enhancement patterns of lesions and the diagnostic performance of CEUS were analyzed.

Results: Arterial hyper-enhancement followed by washout was observed in 92.3% (504/546) of the HCC lesions and 85.7% (234/273) of the ICC lesions on CEUS ($P < 0.05$). Additionally, the ICCs presented contrast washout much earlier than the HCCs, with an average time of 27.5 s after injecting the contrast agent compared with 70.1 s for the HCCs ($P < 0.05$). Peripheral rim-like enhancement was present in 68.5% (187/273) of the ICCs, which was significantly more often than that in the HCCs (2.0%, 11/546) ($P < 0.05$). When using arterial hyper-enhancement with washout later than 43 s after injecting the contrast agent and with no peripheral rim-like enhancement as the diagnostic criteria for HCC ≤ 5 cm in diameter, the area under the curve was 0.808, with 64.1% sensitivity, 97.4% specificity and 73.6% accuracy.

Conclusions: Although ICC may show the typical enhancement pattern of HCC on CEUS, peripheral rim-like enhancement and quick contrast washout show high efficiency in the differential diagnosis of HCC and ICC.

P2-31

Assessment of the Malignant Potential of Hepatocellular Carcinoma Using Kupffer-Phase Images of Contrast-Enhanced Sonography with Sonazoid

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Background/Aim: The gross type of hepatocellular carcinoma (HCC) is associated with malignant potential, and the single nodular with extranodular growth (SNEG) type and the confluent multinodular (CMN) type have poorer prognoses than the single nodular (SN) type. The aim of the present study was to clarify the correlation between gross type and the Kupffer-phase images of contrast-enhanced sonography with Sonazoid.

Methods: A total of 73 patients with HCCs under 5 cm in diameter who underwent Sonazoid ultrasound before hepatic resection were analyzed. The HCCs were classified into two groups according to tumor margin. The irregular type included HCC with an irregular or unclear margin on conventional B-mode or with an irregular margin on the Kupffer-phase images of Sonazoid ultrasound. Malignant potential was also classified based on gross types. SN type was considered low-grade malignancy, and SNEG and CMN types were considered high-grade malignancy.

Results: Thirteen SN type, 32 SNEG type and 28 CMN type were evaluated. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of prediction of high-grade malignancy using irregular type on conventional B-mode were 72% (43/60), 85% (11/13), 96% (43/45), 39% (11/28), and 74% (54/73), respectively. In comparison with conventional B-mode, the corresponding values for prediction of high-grade malignancy using irregular type on the Kupffer-phase images were 93% (56/60), 85% (11/13), 97% (56/58), 73% (11/15), and 92% (67/73), respectively.

Conclusions: The Kupffer-phase images more accurately predict the malignant potential of HCC than conventional B-mode images and can provide essential information to determine the optimal treatment strategy.

P2-32

Usefulness of CEUS and Gd-EOB-DTPA-Enhanced MRI in the Diagnosis of Macroscopic Type of Hepatocellular Carcinoma

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Objective: The macroscopic type of HCC has been reported to be associated with prognosis. This study aimed to compare the diagnostic performance of contrast-enhanced ultrasound (CEUS) with Sonazoid and gadolinium-ethoxybenzyl-diethylenetriamine penetaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) in the assessment of macroscopic findings of hepatocellular carcinoma (HCC).

Methods: A total of 66 surgically resected nodules in 64 patients who underwent both preoperative CEUS and EOB-MRI were analyzed. By using resected apcimens, the HCCs were macroscopically categorized into simple nodular (SN) and non-SN typed of HCC. To estimate macroscopic categorization of 66 HCCs, post-vascular phase of CEUS and hepatobiliary phase of EOB-MRI were evaluated independently and blindly by two hepatologists with more than five years experience in hepatobiliary imaging.

Results: Thirty-eight HCCs were categorized as having SN and the remaining 28 were categorized as non-SN. The areas under the receiver operating characteristic curve (Az) values for the diagnosis of SN did not differ between CEUS and EOB-MRI [reader1: CEUS 0.742, EOB-MRI 0.817, reader2: CEUS 0.742, EOB-MRI 0.773]. The Az value for the combination of the CEUS and EOB-MRI for the diagnosis of SN HCC was 0.856 (reader1) and 0.810 (reader2), resulting in a higher diagnostic value. The Az value for the diagnosis of SN in HCCs >2 cm tend to be greater than the value in HCC ≤2 cm [≤2 cm reader1: CEUS 0.671, EOB-MRI 0.748, CEUS+EOB-MRI 0.781, ≤2 cm reader2: CEUS 0.771, EOB-MRI 0.708, CEUS+EOB-MRI 0.790, >2 cm reader1: CEUS 0.756, EOB-MRI 0.822, CEUS+EOB-MRI 0.903, >2 cm reader2: CEUS 0.761, EOB-MRI 0.767, CEUS+EOB-MRI 0.796].

Conclusion: For the evaluation of macroscopic findings of nodular HCC, CEUS was equal to EOB-MRI and combination of these two modalities yielded a greater diagnostic performance.

P2-33

Quick and Easy Detection Method for US Beginner Using Virtual US

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Objective: Sometimes it is difficult to detect small liver tumor for US and to image positional relationship between the tumor and vessels, especially subcostal view. In this study, we evaluated the usefulness of a new technology, virtual US imaging device as a tool to assist novice sonographers.

Methods: A prospective blinded pilot study was conducted involving patients with liver lesions. Two sonographers and two medical doctors with less than 5 years of experience performed US examinations. Detecting time on US and the success rate for detecting liver lesions with/without using the virtual US imaging device, SYNAPSE VINCENT (Fujifilm Medical Co.), before US examination was evaluated.

Results: 32 patients with the following 42 liver lesions were included: liver cyst (n = 24), hemangioma (n = 8), hepatocellular carcinoma (n = 6), liver metastasis (n = 4). The maximal diameter of these lesions ranged from 0.3 to 1.5 cm (mean ± SD, 0.8 ± 0.4 cm). The average time for detecting liver lesions on US was 47.8 seconds (range: 7–113) with VINCENT and 112.9 seconds (range: 14–313) without VINCENT before US examination. There were significant differences in the duration of US examination with/without VINCENT (p = 0.0002, Student's t-test). The rates for accurately detecting liver lesions were 100% and 76.2% (16/21) in US beginner with/without VINCENT respectively. Significantly higher detection rates in the US beginners were compared to without VINCENT (p = 0.047, Fisher's exact test).

Conclusion: Before US examination, a reference with VINCENT could contribute to the successful detection of liver lesions, even with 1 cm, and time-saving for US beginners. And this technology has led to success in taking clear imaging for CEUS and performing safe RFA therapy.

P2-34

Pathologic Features of Hypointense Hepatocellular Carcinomas on the Apparent Diffusion Coefficient Mapping and the Critical Recurrence After Hepatectomy

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Background: It has been reported that the apparent diffusion coefficient (ADC) value of hepatocellular carcinomas (HCCs) on diffusion-weighted magnetic resonance imaging (MRI) is associated with their histological grade. The present study aimed to evaluate pathologic features of hypointense HCCs on the ADC map, and to elucidate the association between the signal intensity on the ADC map and critical recurrences after hepatectomy.

Methods: Between December 2008 and January 2013, 52 consecutive patients with initial hypervascular HCCs (solitary and ≤5 cm in diameter) without vascular invasion on imaging were examined by diffusion-weighted MRI before hepatectomy. The signal intensities of HCCs on the ADC map were visually compared with the surrounding liver and categorized as hypointense and non-hypointense. Critical recurrence was defined as >3 intrahepatic recurrences, vascular invasion, dissemination, and/or metastasis.

Results: The 52 HCCs were evaluated as hypointense in 26 and non-hypointense in 26. No significant differences were seen in age, gender, etiology, tumor size, and tumor markers levels between hypointense group and non-hypointense group. However, in resected specimens, significant differences were noted in histological grade and microscopic portal invasion between the two groups. The percentages of poorly differentiated HCCs in hypointense group and non-hypointense group were 54% (14/26) and 4% (1/26), respectively. The percentage of microscopic portal invasion in the hypointense group and non-hypointense group was 31% (8/26) and 4% (1/26), respectively. The cumulative 3-year recurrence rates of the hypointense and non-hypointense group on the ADC map were 72% and 48% (p = 0.051), respectively, with cumulative 3-year critical recurrence rates of 56% and 13% (p = 0.001), respectively. Multivariate analyses indicated that hypointensity on the ADC map was the only independent background factor related to critical recurrence after hepatectomy.

Conclusions: The hypointense HCCs on the ADC map are characterized by poorly histological differentiation and more frequent microscopic portal invasion, and they are significantly associated with the critical recurrences after hepatectomy.

P2-35

Evaluation of Hepatocellular Carcinoma on Gadoteric Acid-Enhanced MR Imaging and Contrast-enhanced CT Comparing with Histopathological Examinations

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Background & Aims: Gadoteric acid (gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid; Gd-EOB-DTPA) is a liver-specific hepatobiliary MRI contrast agent that offers both dynamic imaging and liver-specific static hepatocyte imaging of the hepatocyte phase. Some investigators have reported good detection of HCCs in cirrhotic patients on gadoteric acid-enhanced MRI. However, there are few studies have prospectively performed intraindividual comparisons of gadoteric acid-enhanced 3T MRI and MDCT with histopathological examinations, used as a reference standard, for detection of HCCs. The purpose of this study was to prospectively compare the efficacies of gadoteric acid-enhanced 3T MRI and multiphasic contrast-enhanced MDCT with that of histopathological examinations for detection of HCCs in surgical candidates.

Materials and Methods: The study was approved by the institutional review board at each of the 4 centers. Patients were scheduled for undergoing multiphasic CT and gadoteric acid-enhanced MR imaging and also for liver surgery were prospectively included in this study. Diagnostic analysis was performed by sensitivity and positive predictive value (PPV) for the detection of HCCs and characterization between HCCs and benign lesions in MR images compared with CT images.

Results: Fifty-four patients with 83 histopathologically confirmed HCCs were included in this study. The mean tumor size of the 83 HCC was 29 mm, ranging from 5 to 140 mm, and including 19 tumors under 10 mm in diameter. Combined interpretation of dynamic and hepatobiliary phase of gadoteric acid-enhanced MR imaging using 3T showed statistically higher sensitivity in lesion detection (83%) than multiphasic MDCT images (70%; $P < 0.001$), though the mean PPV was not significantly different between MR imaging and CT images (97% and 97%, respectively). The mean Az value for MR imaging (0.927) was significantly higher than that for CT images (0.864, $P < 0.01$).

Conclusions: In this multicenter prospective study, the sensitivity for preoperative detection of HCCs was higher for gadoteric acid-enhanced MRI than for multiphasic MDCT imaging.

P2-36

Hepatocellular Adenoma with Beta-Catenin Activation Shows ISO/Hyperintensity on Hepatobiliary Phase of Gd-EOB-DTPA Enhanced MRI; Usefulness in Predicting Malignant Potentiality

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Background: Hepatocellular adenomas (HCAs) are subclassified into four subtypes according to molecular/genetic characteristics: hepatocyte nuclear factor-1 α inactivated (H-HCA), β -catenin activated (b-HCA), inflammatory (I-HCA) and unclassified HCA (u-HCA). Among them, b-HCA and I-HCA with β -catenin activation have a potentiality of malignant transformation, and therefore, to discriminate it from other types of HCAs is clinically important. It has been reported that b-HCA demonstrated iso/hyperintensity on hepatobiliary phase (HB phase) of Gd-EOB-DTPA MRI (EOB-MRI) with overexpression of organic anion transporter polypeptide (OATP) 1B3 (uptake transporter of Gd-EOB-DTPA). The aim of this study was to evaluate the relationship between OATP1B3 expression and signal intensity on the HB phase of EOB-MRI in HCA with β -catenin activation.

Methods: Immunohistochemically confirmed 6 cases of b-HCAs and one case of I-HCC with internal β -catenin activation were investigated in this study. Immunohistochemical staining for OATP1B3 was performed in 5 cases and was graded semiquantitatively. EOB-MRI was carried out in 5 cases and signal intensity on HB phase of them was evaluated.

Results: Histopathologically, all cases ($n = 4$) of b-HCA and one case of I-HCA with β -catenin activation showed membranous expression of OATP1B3, stronger OATP1B3 expression relative to the surrounding liver in 3 cases and similar in the other two. All 5 cases who received EOB-MRI showed iso/hyperintensity on HB phase of EOB-MRI.

Conclusion: All of HCA with β -catenin activation showed iso/hyperintensity on HB phase of EOB-MRI and equal to stronger membranous expression of OATP1B3 relative to the surrounding liver. Because almost all of non-b-HCAs are reported to demonstrate hypointensity on HB phase, EOB-MRI is considered to be valuable to predict a malignant potentiality of HCAs.

P2-37

Emergence of β -Catenin Mutated HCC During Early-Stage Multi-Step Hepatocarcinogenesis: Observation by Gd-EOB-DTPA Enhanced MRI

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Background and Purpose: It has been verified that there was a highly significant correlation between hyperintensity on hepatobiliary (HB) phase of Gd-EOB-DTPA enhanced MRI (HBP-EOB-MRI) and β -catenin mutation in HCCs because of overexpression of OATP1B3 (OATP8). The purpose of this study is to clarify when hyper-intense (β -catenin mutated) HCC emerges during multi-step hepatocarcinogenesis.

Methods: HBP-EOB-MRI findings of ninety-nine nodules which show low-grade borderline nodule (LBL) pattern on angiography-assisted CT were evaluated. Malignant transformation ratios of these modules were calculated with Kaplan-Meier method. Then HBP-EOB-MRI findings of 73 nodules which shows high-grade borderline nodule (HBL) pattern, namely, shows hypovascular nodule containing hypervascular foci (nodule-in-nodule pattern), were evaluated.

Results: In LBL analysis, 41.4% of the nodules showed hypo-, 42.4% showed iso-, and 16.2% showed hyper-intense on HBP-EOB-MRI. Of the 99 LBL nodules, 78 were followed using multiphasic contrast-enhanced CT/MRI. Progress rates from LBL to hypervascular HCC were 17% in 1-year, 28% in 2-year, and 41% in 3-year in hypo-intense LBL ($n = 32$), 7% in 1-year, 7% in 2-year, and 7% in 3-year in iso-intense LBL ($n = 35$), 0% in 1-year, 0% in 2-year, and 0% in 3-year in hyper-intense LBL ($n = 11$). There are significant differences in progress rates to HCC both in iso- vs. hypo-intense nodules and hyper- vs. hypo-intense nodules ($P = 0.032$ and $P = 0.037$, respectively). In HBL analysis, hypervascular foci of the nodules, which represent de-differentiated portion within the nodule, showed hyperintense on HBP-EOB-MRI in 28.8% ($n = 21$) of the nodules.

Conclusion: Hyperintense HCC on HBP-EOB-MRI (majority of them are β -catenin mutated HCC) emerges from de-differentiated hypervascular foci in HBL during early-stage of multi-step hepatocarcinogenesis, but not from de novo hepatocarcinogenesis.

P2-38

The Prognostic Value of Alpha-Fetoprotein Response for Hepatocellular Carcinoma Treated with Sorafenib Combined with Transarterial Chemoembolization

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Background: Whether the alpha-fetoprotein (AFP) response can predict the survival of hepatocellular carcinoma (HCC) patients treated with the sorafenib combined with transarterial chemoembolization (TACE) remains unclear. This study aimed to evaluate the prognostic value of AFP response in HCC patients treated with combination therapy. Moreover, the correlation between AFP response and imaging response were also examined.

Methods: From May 2008 to July 2012, 118 unresectable HCC patients with the baseline AFP level >20 ng/ml treated with the combination therapy were included. Receiver operating characteristics (ROC) curve was used to generate a cutoff point for AFP changes for predicting survival. The AFP response was defined as an AFP decrease rate [Δ AFP (%)] greater than the cutoff point. The Δ AFP (%) was defined as the percentage of changes between the baseline and the nadir within 1–2 months after combination therapy (Δ AFP (%) = $[(\text{AFP}_{\text{baseline}} - \text{AFP}_{\text{post-treatment}}) / \text{AFP}_{\text{baseline}}] \times 100\%$). Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST (mRECIST) criteria were used for radiological evaluation.

Results: The median follow-up time was 8.8 months (range 1.2–66.9). 49 (41.5%) patients with Δ AFP (%) $>46\%$ were classified into in AFP response group and 69 (58.5%) patients with Δ AFP (%) $<46\%$ were classified into non-response group. Most baseline clinical characteristics were not significantly different between AFP response and non-response groups, but the proportion of males was higher in AFP response group than in non-response group. For the ROC curve, AFP level reduction of 46% was identified as the cutoff point (sensitivity = 53.7%, specificity = 83.3%). In this study, 49 patients with Δ AFP (%) $>46\%$ were classified into in AFP response group and 69 patients with Δ AFP (%) $<46\%$ were classified into non-response group. Most baseline characteristics were not significantly different between AFP response and non-response groups. The median overall survival was significantly longer in AFP response group than in AFP non-response group (12.8 vs. 6.4 months, $P = 0.001$). For 84

patients with radiological evaluation, AFP response was significantly associated with mRECIST criteria response ($P = 0.002$), but not RECIST criteria response ($P = 0.606$). Of the 34 patients without radiological evaluation, 8 and 26 patients were in AFP response and AFP non-response groups, respectively. The median OS was significantly longer in AFP response group than in AFP nonresponse group (11.3 vs. 3.9 months, $P = 0.002$).

Conclusions: AFP response could predict the survival of patients with unresectable HCC treated with combination therapy.

the HCC patients comprise 100 TNM stage1, 16 stage2, 44 stage3 and 14 stage4 cases. A group of healthy donors was included as the control ($n = 50$).

Results: The level of PIVKAI1 in HCC patients is significantly higher than that in CHB, liver cirrhosis patients and healthy control group ($P < 0.001$, respectively). Furthermore, PIVKAI1 level in HCC stage1 patients was significantly higher than that in CHB, liver cirrhosis and healthy control group ($P < 0.001$, respectively). The threshold of PIVKAI1 for predicting HCC was 25.47 mAU/ml (sensitivity 72.52%, specificity 88%).

Conclusions: We demonstrated the feasibility of developing a noninvasive biomarker of early stage of HCC. PIVKAI1 may serve as an index for diagnosis of HCC.

P2-39

The Diagnostic Value of PIVKA II for Primary Hepatocellular Carcinoma

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Background: The survival of patient with hepatocellular carcinoma (HCC) is poor because the diagnosis is often too late when curative treatment is not possible. Early detection of HCC is critical for treatment outcome and survival; however there are lack of noninvasive early diagnostic biomarkers to date. In this study, we evaluate the diagnostic value of protein induced by vitamin K absence or antagonist-II (PIVKAI1).

Methods: Cross-section analysis of the PIVKAI1 level in serum was performed using the Lumipulse G PIVKAI1 assay in 49 chronic hepatitis B (CHB), 51 hepatitis B virus (HBV)-related liver cirrhosis and 174 HBV-related HCC patients. And

P2-40

Utility of Microvesicles as Plasma Biomarkers in Patients with Hepatocellular Carcinoma

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Introduction: Hepatocellular carcinoma (HCC) is a hypervascular neoplasm with high levels of apoptosis and necrosis. To date there has been a paucity of early diagnostic plasma biomarkers for HCC. Microvesicles (MV) are sub-micron vesicles secreted from cell plasma membrane in both physiological and pathological states. We investigated the utility of MV as a diagnostic and prognostic biomarker for HCC.

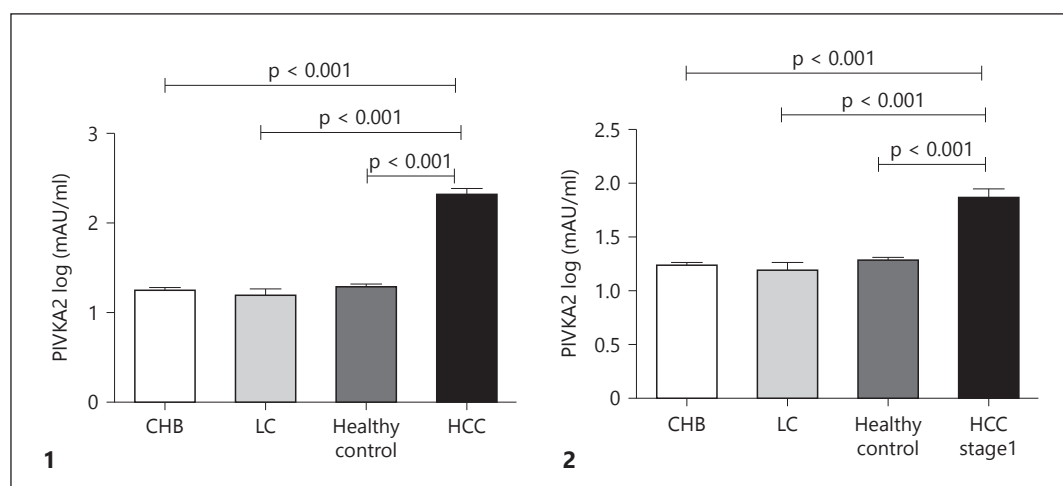


Fig. 1. Comparison of PIVKAI1 amongst healthy control, CHB, liver cirrhosis, and HCC groups.

Fig. 2. Comparison of PIVKAI1 amongst healthy control, CHB, liver cirrhosis, and HCC stage1 groups. (for Abstract P2-39).

Methods: Fresh blood samples were collected from patients attending the Hepatology Clinic at Royal Prince Alfred Hospital, Sydney, Australia. These include patients with hepatocellular carcinoma ($n = 12$), patients with hepatic cirrhosis ($n = 11$), and normal healthy volunteers ($n = 6$). Blood was processed immediately by centrifuging at 200 g for 10 minutes followed by 10,000 g for 20 minutes to derive platelet-free plasma, which was then centrifuged for 100,000 g for 90 minutes to pellet MVs. The MV pellets were resuspended in 0.1 micron-filtered PBS and diluted (1:50) prior to being analysed on the NanoSight LM10-HSBFT Nanoparticle Characterisation System. Biochemical and clinical data of these patients were also recorded, including liver function tests, full blood counts, coagulation studies, AFP, tumour activity on imaging, creatinine, Child-Pugh and MELD scores, and disease aetiology. Significance testing was performed using unpaired ttests between groups.

Results: Microvesicle secretion into plasma of HCC patients is elevated 3.4 fold compared with normal human plasma (mean particle concentration: $518.4 \pm 81 \times 10^6$ vs. $154.1 \pm 31 \times 10^6$ /ml, $p < 0.001$) and 2.5 fold compared with cirrhotic patients' plasma ($518.4 \pm 81 \times 10^6$ vs. $205.0 \pm 29 \times 10^6$ /ml, $p < 0.003$); there is no difference between normal and cirrhotic patient plasma MV concentration ($154.1 \pm 31 \times 10^6$ vs. $205.0 \pm 29 \times 10^6$ /ml, $p = 0.25$). There is no significant variation between the MV sizes of the three groups. Analysis of MV in HCC and liver cirrhosis patients were further stratified by MELD score (>15 or <15); in HCC patients, plasma MV concentration was increased by 2.4 fold in the MELD <15 group compared with MELD >15 ($607.1 \pm 268 \times 10^6$ vs. $252.6 \pm 47 \times 10^6$ /ml, $p = 0.05$), whereas in the cirrhosis group stratifying by MELD did not show a difference between plasma MV concentration ($251.5 \pm 77 \times 10^6$ vs. $187.6 \pm 103 \times 10^6$ /ml, $p < 0.003$). Subgroup analyses were performed by stratifying plasma MV concentration by tumour activity as diagnosed by imaging and by AFP levels, and neither was significant.

Conclusion: Plasma MV secretion is significantly increased in HCC patients compared to cirrhosis and normal plasma. When stratified by MELD score, HCC patients with low MELD score (<15) had significant elevation of plasma MV concentration compared with patients with high MELD score (>15). There is no such trend in the plasma MV concentration of the cirrhosis group. Therefore, plasma MV concentration may be useful as a diagnostic biomarker for HCC in patients with low MELD scores.

P2-41

Tumor Markers AFP, AFP-L3, and DCP in Refractory to Transcatheter Arterial Chemo-Embolization Against Hepatocellular Carcinoma

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Background/Aim: We examined tumor marker levels to judge more detailed transcatheter arterial chemoembolization (TACE)-refractory hepatocellular carcinoma (HCC).

Materials/Methods: We enrolled patients treated from 2000 to 2011 for HCC beyond Milan criteria who had Child-Pugh A, and were without portal vein thrombosis and metastasis ($n = 154$). Modified TACE-refractory criteria of the Liver Cancer Study Group of Japan (m-LCSGJ), from which the tumor marker item was excluded, and ART-score were used for judging TACE-refractory. Alpha-fetoprotein at ≥ 100 ng/ml, fucosylated alpha-fetoprotein $\geq 10\%$, and des-gamma-carboxy prothrombin ≥ 100 mAU/ml were used to define positive. We added up the number of positive tumor markers as a prognostic score for judging more detailed evaluation of TACE-refractory.

Results: For dividing patients into refractory and non-refractory groups, m-LCSGJ [MST 27.1 vs. 50.0 months ($P < 0.001$)] was superior to ART-score [MST 22.0 vs. 35.1 months ($P = 0.051$)]. In the refractory-group by m-LCSGJ, patients with low score of positive tumor marker (<2) after 2 sessions of TACE ($n = 36$) showed better prognosis than the others ($n = 72$) (MST 37.7 vs. 23.2 months, $P = 0.014$).

Conclusion: Non-refractory by m-LCSGJ criteria had better response and the number of tumor marker score (≥ 2) is an easy method for predicting response to TACE and for more detailed evaluation of TACE-refractory.

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Double or Triple Positive Tumour Markers Can Predict Outcome in Patients with Hepatocellular Carcinoma After Radiofrequency Ablation

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Background: Few reports have shown the relevance of the tumour markers alpha-fetoprotein, Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein, and des-γ-carboxy prothrombin, with regard to outcome for radiofrequency ablation (RFA) in patients with hepatocellular carcinoma (HCC). We evaluated the therapeutic effect of RFA according to the expression of these markers.

Methods: Between October 2007 and October 2012, 323 patients underwent RFA for HCC at the Department of Gastroenterological Surgery, Kumamoto University Hospital (Kumamoto, Japan). The patients with ≤3 HCC lesions and lesions ≤3 cm in diameter on preoperative hepatic imaging findings; and confirmation of sufficient ablation area (adequate ablation margin >5 mm) with no enhancement on contrast-enhanced CT one month after RFA was included and finally 160 patients who underwent percutaneous and surgical RFA for HCC were analyzed. Patients were divided into negative (n = 51), single (n = 69), double (n = 31), and triple positive (n = 9) groups according to the pre-treatment expression of tumour markers. Any relationships between clinical parameters, outcomes, and tumour markers were determined.

Result: There were significant difference in the levels of HCV-Ab ($P = 0.004$), platelet count ($P = 0.045$), and serum albumin ($P < 0.001$) between the 4 groups. The 3-year recurrence-free and overall survival of the negative, single, double, and triple positive groups were 30%, 19%, 16%, and 11% ($P = 0.022$), and 94%, 88%, 67%, and 37% ($P < 0.001$), respectively. The 2-year local recurrence rates were 6.5%, 0%, 41.2%, and 61.9% respectively ($p < 0.0001$), but there was no significant difference between patients with double and triple positive tumour makers ($P = 0.143$). Multivariate analysis

revealed that a double or triple positive pre-treatment tumour marker profile was independently associated with local recurrence (hazard ratio = 4.85; 95% confidence interval = 1.945–12.048; $P < 0.001$) and overall survival (hazard ratio = 4.21, 95% confidence interval: 1.891–9.370, $P < 0.001$). Multivariate analysis indicated that low serum albumin (HR 3.44; 95% CI 1.410–8.403; $P = 0.007$), ≥2 tumours (HR 2.21; 95% CI 1.025–4.405; $P = 0.043$), and ≥2 tumour markers (HR 4.21; 95% CI 1.891–9.370; $P < 0.001$) were independent risk factors associated with poor OS.

Conclusion: RFA should not be performed in patients with HCC who exhibit pre-treatment expression of ≥2 of these tumour markers.

P2-43

The Role of Alpha-Fetoprotein Ratio in BCLC C Hepatocellular Carcinoma Patients Undergoing Sorafenib Treatment

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Background: Alpha-fetoprotein (AFP) is a simple tumor marker and associated with prognosis for hepatocellular carcinoma (HCC). Whether AFP ratio associated with tumor response and survival in BCLC C patients under sorafenib treatment is unclear. We investigated the correlation between AFP ratio with modified Response Evaluation Criteria in Solid Tumors (mRECIST), time to disease progression (TTP) and, overall survival (OS) in advanced HCC patients undergoing sorafenib treatment.

Methods: A total of 196 BCLC C HCC patients from Taipei Veterans General Hospital who underwent sorafenib treatment from 2012 to 2013 with available AFP levels and contrast-enhanced image studies at baseline and follow-up were retrospectively reviewed. One hundred fifty patients

Table 1. AFP ratio Correlate with tumor response at 2 months to sorafenib in patients with baseline AFP ≥20 ng/ml (for Abstract P2-43)

	Partial response	Stable disease	Progressive disease	p
All patients (n = 150)	9 (6%)	71 (47.3%)	70 (46.7%)	
AFP ratio (median, range)	0.55 (0.06, 3.37)	1.14 (0.01, 25.84)	2.08 (0.08,44.32)	0.003
AFP ratio ≤1	6 (66.7%)	33 (46.5%)	18 (25.7%)	0.008

had AFP ≥ 20 ng/ml at baseline. AFP ratio was measured at 2 months post sorafenib treatment. Tumor response was evaluated by mRECIST criteria according to contrast-enhancing images at 2 months interval. TTP and OS were calculated according the chart records.

Results: The median TTP and OS of the 196 patients were 3.3 and 8.7 months. Among the 150 patients with baseline AFP ≥ 20 ng/ml, the median TTP, OS, and AFP ratio were 2.7 months, 6.4 months and 1.42, respectively. Fifty-seven patients (38%) had AFP ratio ≤ 1 . The sensitivity and specificity of AFP ratio ≤ 1 to predict tumor response according to mRECIST criteria were 48.75% and 74.29%. The median TTP were 4.8 and 2.1 months in patients of AFP ratio ≤ 1 and >1 . The hazard ratio (HR) of TTP for AFP ratio ≤ 1 was 0.513 ($p = 0.001$). The median OS were 9.1 and 5.4 months in patients of AFP ratio ≤ 1 and >1 . The HR of OS for AFP ratio ≤ 1 was 0.529 ($p = 0.002$). In multivariate analysis, AFP ratio ≤ 1 was independent good prognostic factor.

Conclusion: AFP ratio at 2 months could not replace contrast-enhanced study in evaluating tumor response. But, AFP ratio at 2 months can be a prognostic marker representing better TTP and OS.

P2-44

Caveolin-1 Confers Resistance of Hepatoma Cells to Anoikis by Activating IGF-1 Pathway

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Background/Aims: Anoikis resistance is a prerequisite for hepatocellular carcinoma (HCC) metastasis. The role of Caveolin-1 (CAV1) in anoikis resistance of HCC remains unclear.

Methods: The oncogenic effect of CAV1 on anchor-independent growth and anoikis resistance was investigated by overexpression and knockdown of CAV1 in hepatoma cells. IGF-1 pathway and its downstream signals were detected by immunoblot analysis. Caveolae invagination and IGF-1R internalization was studied by electron microscopy and ^{125}I -IGF1 internalization assay, respectively. The role of IGF-1R and tyrosine-14 residue (Y-14) of CAV1 was explored by deletion experiment and mutation experiment, respectively. The correlation of CAV1 and IGF-1R was further examined by immunochemical analysis in 120 HCC specimens.

Results: CAV1 could promote anchor-independent growth and anoikis resistance in hepatoma cells. CAV1-overexpression increased the expression of IGF-1R and subsequently activated PI3K/Akt and RAF/MEK/ERK pathway, while CAV1 knockdown showed the opposite effect. The mechanistic study revealed that CAV1 facilitated caveolae invagination and ^{125}I -IGF1 internalization. IGF-1R deletion or Y-14 mutation reversed CAV1 mediated anchor-independent growth and

anoikis resistance. In addition, CAV1 expression was positively related to IGF-1R expression in human HCC tissues.

Conclusion: CAV1 confers resistance of hepatoma cells to anoikis by activating IGF-1 pathway, providing a potential therapeutic target for HCC metastasis.

P2-45

ID1 Mediated Pentose Phosphate Pathway Activation in Hepatocellular Carcinoma Confers Resistance to Oxaliplatin

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Background: Development of drug resistance is one of the major concerns of hepatocellular carcinoma yet mechanistic understanding and therapeutic options remain limited. Here we show that aberrant high expression of inhibitor of differentiation 1 (ID1), a dominant negative regulator of basic helix loop helix transcription factor, activates pentose phosphate pathway in hepatocellular carcinoma and confers resistance to oxaliplatin-induced apoptosis.

Methods: MHCC97H-OXA, an oxaliplatin-resistant cell line was established. DNA microarrays were used to measure changes in gene expression as a result of oxaliplatin treatment. Aberrant high expression of ID1 was detected in MHCC97H-OXA cell line. ID1 impacts on oxaliplatin-resistance were evaluated by CCK-8 assay and flow cytometry analysis. By stable transfection, we successfully silenced ID1 expression in MHCC97H-OXA cells line. The underlying mechanics of ID1 induced oxaliplatin-resistance were further studied.

Results: Silenced ID1 expression in MHCC97H-OXA promoted cell apoptosis induced by oxaliplatin. PCR array showed ID1 knockdown significantly decreased the expression of glucose-6-phosphate dehydrogenase (G6PD), a key enzyme in pentose phosphate pathway. Furthermore, silence of ID1 blocked the activation of G6PD, decreased the product of pentose phosphate pathway NADPH, augmented reactive oxygen and species (ROS) thus induced cell apoptosis. Recovery of G6PD expression in MHCC97H-OXA ID1 knockdown cell line reversed this process and induced cells resistance to oxaliplatin. Luciferase assay and co-immunoprecipitation assay demonstrated ID1 interacted with the transcription factor c-Myc, co-activated G6PD promoter and promoted its transcription.

Conclusions: Our study provides the first evidence that ID1 contributes to oxaliplatin resistance in hepatocellular carcinoma by activation of the pentose phosphate pathway. This newly defined pathway has important implications for developing new therapeutic interventions for better efficacy of anti-cancer drugs.

P2-46

Synergistic Anticancer Effect of Metformin in Combination with Immunosuppressant on Hepatocellular Carcinoma Cell Lines

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After liver transplantation (LT), immunosuppression is needed to avoid rejection and graft loss, however, it can stimulate hepatocellular carcinoma (HCC) recurrence and progression. Previous studies have shown that metformin had an anticancer effect on several cancers, including HCC. The aim of this study was to evaluate the interactions between metformin and immunosuppressive agents including sirolimus, tacrolimus and mycophenolate mofetil (MMF) for anti-tumor activity. Cell viability was determined using a MTT assay and western blot analysis for mammalian target of rapamycin (mTOR) pathway related proteins were performed to reveal their mechanism. Metformin and sirolimus had synergistic antiproliferative effect and the combination of metformin, sirolimus and MMF also showed synergistic antiproliferative effect in specific HCC cells. Synergistic effect of metformin and sirolimus through the inhibition of mTOR and its down-stream, p70S6K, and p-4EBP1 were demonstrated. Metformin and sirolimus also showed synergistic effect for the down-regulation of Livin and Survivin expressions in HepG2 and Hep3b cells. In conclusion, metformin had synergistic interactions with sirolimus in terms of anticancer effects for HCC cells and the mechanism explaining this synergistic inhibition might be related with mTOR pathway. These results may provide a foundation for further studies for patients with HCC who underwent LT in clinical era.

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Cyclin E1 Inhibition Can Overcome Sorafenib Resistance in Hepatocellular Carcinoma Cells Through Mcl-1 Suppression

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Background: Cyclin E1 suppression by sorafenib, which is independent of effects on mitogen-activated protein kinase-extracellular signal-regulated kinase/extracellular signal-regulated kinase signaling, was found to correlate with sorafenib sensitivity of hepatocellular carcinoma (HCC) cells.

Methods: Effects of cyclin E1 suppression on sorafenib-induced apoptosis were tested in both sorafenib-sensitive (Huh-7, HepG2) and sorafenib-resistant (Huh-7R and HepG2R) HCC cells. Activity of pertinent signaling pathways and expression of cell cycles- and apoptosis-related proteins were measured by Western blotting. The downstream mediators of apoptosis were explored by transient transfection and RNA-interference experiments. Efficacy of sorafenib combined with the pan-cyclin-dependent kinase inhibitor flavopiridol was tested by xenografts experiments.

Results: Cyclin E1 mRNA and protein expressions were suppressed after sorafenib treatment in sorafenib-sensitive but not in sorafenib-resistant HCC cells. Changes in cyclin E2 or D1 were not correlated with sorafenib sensitivity. Knockdown of cyclin E1 expression reversed the resistance of HCC cells to sorafenib in terms of cell growth and apoptosis induction, whereas over-expression of cyclin E1 increased the resistance of HCC cells to sorafenib. The growth-inhibitory and apoptosis-inducing effects of sorafenib were enhanced by the pan-cyclin-dependent kinase (CDK) inhibitor flavopiridol, and Mcl-1 suppression was found to play important roles in mediating this enhancing effect.

Conclusion: Cyclin E1 suppression in HCC cells may serve as a pharmacodynamic biomarker to predict sorafenib efficacy. Combination of sorafenib and CDK inhibitors may improve the therapeutic efficacy of sorafenib in HCC.

P2-48

Inhibition of Discoidin Domain Receptor 2 May Enhance the Antitumor Effect of Sorafenib in a Hepatocellular Carcinoma Patient-Derived Xenograft (PDX) Model

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Background: Discoidin domain receptors (DDR2) have recently been identified as tyrosine kinase receptors for collagen, a key constituent of the extracellular matrix. Our previous study demonstrated that the suppression of DDR2 inhibited the growth of hepatocellular carcinoma (HCC) cells in a cell-type dependent manner. In this study, we investigated the possibility of a synergistic antitumor effect of sorafenib and DDR2 siRNA in an HCC PDX model.

Methods: Fresh HCC tissues were obtained from patients and implanted subcutaneously into immunodeficient mice. To use PDX mice, tumor tissue was serially transplanted for 3–7 generations and subsequently implanted into 5–6 week-old male BALB/c-nude mice. HCC tumor-bearing mice were treated with sorafenib (50 mg/kg by oral gavage daily) and/or DDR2 siRNA, alone or in combination. DDR2 siRNA was

administered by intratumoral injection once in two days, for a total of 6 to 8 doses. At the end of the study, the mice were sacrificed, their body weight and tumor weight were recorded, and the tumors were harvested for analysis.

Results: Three PDX models were available for this study. Sorafenib treatment alone significantly inhibited tumor growth in PDX models 1 and 2. Compared to the treatment with sorafenib alone, the combination treatment with DDR2 siRNA and sorafenib significantly increased the anti-tumor effect ($p < 0.05$) in only PDX model 1. In PDX model 3, the combination treatment showed an increase in the anti-tumor effect, but this was not statistically significant. In PDX model 2, the combination treatment did not show an increase in the anti-tumor effect. Clinical review for patients characteristics was currently underway.

Conclusions: The combination treatment of sorafenib and DDR2 siRNA showed an anti-HCC tumor effect in one of three PDX models. Inhibition of DDR2 may be useful in enhancing the anti-HCC tumor effect of sorafenib in a patient-dependent manner.

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Cyclin Dependent Kinase Inhibitor Dinaciclib Has Potent Activity Against Hepatocellular Carcinoma

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Background: Treatment options for advanced hepatocellular carcinoma (HCC) are limited. Sorafenib remains the only approved therapy, and novel treatment is warranted for advanced HCC. Previous studies reported that inhibition of cyclin dependent kinases (CDKs), especially CDK1, 2, and 9, showed activity against HCC. Dinaciclib is a potent inhibitor of CDK1, 2, 5, and 9 and has an acceptable safety profile in humans. We thus examined the efficacy of *dinaciclib* in HCC.

Methods: In a panel of HCC cell lines including Huh7, HepG2, Hep3B, PLC5, HLE, SKHep1, SNU387, SNU449, SNU423, and SNU475, dinaciclib was examined for its effect on cell viability, cell cycle distribution, and apoptosis induction. The expressions of CDKs, phospho- (p-) Rb (the target of CDK1 and 2), p-ERK (the target of CDK5), c-myc, and p-RNA polymerase II (the target of CDK9) were evaluated. The *in vivo* efficacy of dinaciclib on HCC was tested in mouse xenografts of Huh7 cells implanted subcutaneously.

Results: Dinaciclib showed potent anti-proliferative activities in HCC cell lines. The IC50s to dinaciclib by the MTT assay ranged from 8.5 nM (for Huh7) to 20.1 nM (for SNU475). A low

IC50 was moderately correlated with high baseline cell expression of RNA polymerase II ($r = -0.649$), CDK2 ($r = -0.492$), p-Rb ($r = -0.446$), and c-myc ($r = -0.424$). After 48 hours of dinaciclib treatment, Huh7 cells showed G2/M arrest in a dose-dependent manner. Apoptosis assays including sub-G1 fraction analysis, DNA fragmentation detection, and cleaved PARP-1 confirmed the occurrence of apoptosis in Huh7 cells treated with dinaciclib. Dinaciclib at the concentration near the IC50 inhibited the phosphorylation of Rb, RNA polymerase II, and ERK in Huh7 cells; it also inhibited the expressions of multiple anti-apoptotic proteins including Mcl-1, XIAP, and survivin in Huh7 cells. In xenograft studies, mice receiving dinaciclib had a significantly slower tumor growth rate compared with mice receiving vehicles. Mice tolerated the dinaciclib treatment well without significant body weight change.

Conclusions: Dinaciclib appears to be active against HCC, and further clinical studies are warranted.

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Regulation of Human Hepatocellular Carcinoma Progression by P2X7 Purinergic Receptor

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Introduction: P2X7 receptor (P2X7R) is a transmembrane ligand-gated ion channel receptor activated by extracellular ATP. P2X7R is expressed in a wide variety of normal and disease-associated cell types with play important roles in inflammation, immunity, bone homeostasis, neurological function and neoplasia. But it's biological function in hepatocellular carcinoma (HCC) progression still unclear. The aim of this study is to investigate the role of P2X7R in Human hepatocellular carcinoma cell.

Methods: The P2X7R expression in HCC cell line and HCC tissues was performed immunoblot. Cell viability of knockdown P2X7R to human SK-Hep-1 and Huh-7 cell line was using MTT assay. Cell cycle was determined by flow cytometry. Cell migration and invasion were examined by boyden chamber assay. To identify the potential targets of this P2X7R, human proteinase array analysis was performed. The activities and expression of molecular proteins were measured by immunoblot and RT-PCR. The interaction between proteins and DNA were identifying by Chromatin Immunoprecipitation (ChIP) assay.

Results: Our data showed that P2X7R protein expressions are higher in HCC cells than in normal hepatic cells. The inhibitory effects of P2X7R on HCC cells growth were associated with the G0/G1 cell cycle arrest concomitant with a marked

inhibition of SKP2 and cyclin D1 as well as the induction of the p27 and p21. P2X7R knockdown in Huh-7 and SK-Hep-1 cells decreased cell migration and invasion. Moreover, P2X7R knockdown decreased Akt activity-promoted migration and invasion. si-P2X7R cells treatment with an Akt inhibitor LY294002 in HCC cells inhibited the migration and invasion. Conversely, Akt overexpression in shP2X7R cells produced the opposite effect. In addition, knockdown of P2X7R inhibited the protein and mRNA of KLK10 expression, which are known to contribute to HCC progression.

Conclusion(s): P2X7R may be involved in malignant progression of HCC, and AKT is an important downstream signaling molecule that plays an essential role in mediating P2X7R induced cell proliferation, migration and invasion.

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Beta- and Gamma-mangostin Suppresses the Migration and Invasion of Human Hepatocellular Carcinoma Cells

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Introduction: Beta-mangostin and gamma-mangostin are xanthone derivative that has been shown to have anti-cancer and anti-inflammation properties. The aim of this study investigates the molecular mechanism of the anti-tumor effects of beta-mangostin and gamma-mangostin on human hepatocellular carcinoma cells.

Methods: The cell viability was measured by MTT assay to analyse the effect of drug treatment. Using flow cytometry analysis the cell cycle distribution, and detected the migration and invasion cells by boyden chamber assay. The activities and expression of molecular proteins were measured by Western blotting and RT-PCR.

Results: The results indicated beta-mangostin and gamma-mangostin were no effect of the cell viability of HCC cells under non-cytotoxic concentration. We observed that beta-mangostin and gamma-mangostin exhibited effective inhibition of cell migration and invasion ability of Huh7, SK-Hep-1 and HA22T/VGH cells. Furthermore, Our results revealed that the cells presented an increase in the distribution of hypodiploid phase after a 24-h treatment with beta-mangostin and gamma-mangostin. Beta-mangostin and gamma-mangostin were also found to significantly inhibit the protein and mRNA expression of MMP2, MMP9, epithelial-mesenchymal transition marker N-cadherin, and vimentin and increased the expression of E-cadherin. Moreover, beta-mangostin and gamma-mangostin inhibited a sustained activation of p38 mitogen-activated protein kinase phosphory-

lation, and treatment with a p38 MAPK inhibitor SB203580 were enhance inhibitory of metastasis ability in Huh7 and SK-Hep-1 cells.

Conclusion: These findings demonstrate that a critical role for p38 inhibition in the beta-mangostin and gamma-mangostin-inhibited migration and invasion of human hepatocellular carcinoma cells, and may open interesting perspectives to the strategy in human hepatocellular carcinoma treatment.

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Regulation of Human Hepatocellular Carcinoma Progression by Epithelial Membrane Protein-3

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Background: Epithelial membrane protein 3 (EMP3) is a trans-membrane signaling molecule with important roles in the regulation of differentiation, proliferation and invasion of cancer cells, but its function in hepatocellular carcinoma (HCC) progression remain unclear.

Methods: Immunohistochemistry, immunofluorescence and western blot analysis was performed for EMP3 in human hepatocellular carcinoma tissues and four HCC cells. Cell viability of knockdown EMP3 to human SK-Hep-1 and Huh-7 cells lines was examined using MTT assay. Cell cycle distribution was determined by flow cytometry. Cell motility, migration and invasion was examined by wound healing assay, migration and invasion assay. Expression of cell cycle-regulated proteins, MMP-9 and uPA was examined at mRNA (RT-PCR), activity (Gelatin/Casein zymography) and protein (western blot) levels.

Results: Our data showed that EMP3 protein and mRNA expression are higher in HA22T/VGH, SKHep-1 and Huh-7 cells than in HepG2 cells, and it was significantly up-regulated in HCC tissues compared the non-tumor HCC tissue. The inhibitory effects of EMP3 on HCC cells growth were associated with the G0/G1 cell cycle arrest concomitant with a marked inhibition of SKP2 and cyclin E as well as the induction of the p27. EMP3 knockdown in HA22T/VGH and SK-Hep-1 cells decreased cell motility, migration and invasion. Knockdown of EMP3 also decreased the protein and activity levels of MMP-9 and uPA in HCC cells. Moreover, EMP3 knockdown decreased Akt activity-promoted migration and invasion. In addition, shEMP3 cells treatment with an Akt inhibitor LY294002 in HCC cells inhibited the migration and invasion. Conversely, Akt overexpression in shEMP3 cells produced the opposite effect.

Conclusion(s): EMP3 may be a novel oncogene in HCC, and its downregulation may effectively suppress HCC tumor growth and metastasis. Targeted inhibition of EMP3 may be a novel therapy for HCC progression.

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Aurora B Kinase Is a Promising Therapeutic Target for Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma (HCC) is one of the most common causes of cancer related death in the world. A major obstacle to the treatment of HCC is the high frequency of tumor recurrence even after curative resection. Patterns of hepatocellular carcinoma (HCC) recurrence after curative surgical resection hold the key to patient prognosis. Our previous study identified Aurora B kinase overexpression as the only independent predictor for aggressive recurrence of HCC. We evaluated the therapeutic potential of inhibition of Aurora B kinase and explored promising combination therapies with inhibition of Aurora B kinase as a treatment for human HCC.

Methods: Human HCC cell lines were analyzed for Aurora B kinase expression. The efficacy of inhibition of Aurora B kinase was evaluated by utilizing the small molecule of selective Aurora B kinase inhibitor. In order to explore combination therapy with inhibition of Aurora B kinase, Bcl-xL/2 inhibitor and Aurora/VEGFR dual kinase inhibitor were utilized *in vitro* and *in vivo*. The *in vivo* effects of aurora B kinase inhibitor and combination therapy targeting the specific molecules were not analyzed only in a subcutaneous xenograft model and also orthotopic model of HCC, in order to investigate the efficacy within the liver microenvironment.

Results: Aurora B kinase expression varied between the human HCC cell lines. Aurora B kinase inhibitor suppressed histone H3 phosphorylation and reduced cell proliferation *in vitro*. Growth of subcutaneous human HCC xenografts was significantly inhibited by administration of Aurora B kinase inhibitor. Significant suppression of liver tumor growth was also observed in orthotopic liver xenografts without a severe adverse effect. Bcl-xL was specifically overexpressed in Aurora B kinase inhibitor induced polyploid HCC cells. The combination of Aurora B kinase inhibitor followed by Bcl-xL/2 inhibitor induced synergistically cellular apoptosis and growth inhibition *in vitro*. In subcutaneous human HCC xenografts, combination therapy of Bcl-xL/2 inhibitor and Aurora

B kinase inhibitor induced significant intratumoral apoptosis and remarkable anti-tumor effects without a severe adverse effect compared with the monotherapy. Aurora/VEGFR dual kinase inhibitor remarkably reduced tumor growth in subcutaneous human HCC xenografts. In orthotopic liver xenografts, the treatment with significantly suppressed *in vivo* phosphorylation of histone H3, vessel formation, normoxic area and hepatoma growth.

Conclusion: Our preclinical studies indicate that Aurora B kinase is a promising therapeutic target for the treatment of HCC.

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Gene Expression Profiling of Cancer Stem Cell Under Hypoxia

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Background/Aim: Cancer stem cells (CSC), with unlimited self-renewal potential and other stem cell characteristics, occur in several types of cancer, including Hepatocellular carcinoma (HCC). Although CSCs can cause tumor initiation, malignant proliferation, relapse and multi-drug resistance, ways to activate them remain unknown. This study aims to evaluate whether CSC acquired tumorigenic characters under tumor hypoxia analyzed by microarray analysis.

Methods: In this study, purified CSCs were isolated from the HCC patients and an Affymetrix microarray was used to investigate their gene expression profile. The results were validated by real-time polymerase chain reaction (PCR).

Results: The results of the microarray indicated that 18 genes were up-regulated and 10 genes were down-regulated in the CSCs. Certain genes that may be significant in the regulation of CSCs, such as HCC were identified. Up-regulated genes almost related metabolism, angiogenesis and hypoxia induced genes. Down-regulated genes related apoptosis and inflammation.

Conclusion: These results may aid the studying of the mechanisms through which CSCs acquire their distinctive properties. Tumorigenic properties of CSCs have a stake in hypoxic stimulation.

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SOX9 Is a New Cancer Stem Cell Marker in Human Hepatocellular Carcinoma

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Backgrounds: Cancer stem cells (CSCs) have a potential role to play the establishment of new therapeutic strategies. Although sex determining region Y-box 9 (SOX9) is known to be an important marker in normal liver development, the relationship between SOX9 and CSCs of hepatocellular carcinoma (HCC) is unclear. Therefore, we aimed to determine if SOX9 can use as a new CSC marker in HCC.

Methods: We transfected the SOX9 promoter-driven enhanced green fluorescence protein gene into HCC cell lines, and investigated fluorescence-activated cell sorting (FACS)-isolated SOX9+/SOX9- cells. We examined SOX9 expression of 166 human primary HCC specimens and 11 extrahepatic HCC metastatic tissues using immunohistochemistry, and analyzed the serum osteopontin level of SOX9+/SOX9- patients.

Results: FACS-isolated single SOX9+ cells showed the ability to self-renew and differentiate into SOX9- cells, while single SOX9- cells never produced SOX9+ cells. SOX9+ cells displayed significantly greater proliferation capacity, higher sphere forming ability, and stronger 5-fluorouracil resistance in vitro. Xenotransplantation in immunodeficiency mice revealed that SOX9+ cells could reproduce themselves, differentiate into SOX9- cells, and generate larger tumors at a higher frequency in vivo. SOX9+ cells were found to be involved in EMT and activation of transforming growth factor beta (TGFβ)/Smad signaling. SOX9+ cells showed higher osteopontin expression than SOX9- cells, and this property was suppressed by SOX9 knockdown via RNA interference. SOX9+ HCC patients had significantly poorer recurrence-free survival, stronger venous invasion, and higher serum osteopontin level than SOX9- patients. SOX9 expression was strongly correlated with osteopontin expression in both primary HCC and metastatic HCC regions. Additionally, co-expression of SOX9 and osteopontin were detected more frequently in metastatic HCC regions than in primary HCC regions.

Conclusions: SOX9+ cells possess cancer stem cell properties correlated with EMT and TGFβ/Smad signaling in human HCC. Osteopontin should be expected the clinical application as a useful surrogate marker of SOX9.

P2-56

Loss of Fbxw7 Expression Is Associated with Poor Prognosis in Intrahepatic Cholangiocarcinoma Regulating Cell Proliferation, Apoptosis and EMT

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Backgrounds: Fbxw7 acts as a tumor suppressor gene by targeting several oncogenic regulators of proliferation, growth and apoptosis for proteasomal degradation. However, the significance of this protein is not yet well understood in intrahepatic cholangiocarcinoma (IHCC). In this study, we aimed to investigate the correlation between Fbxw7 expression and clinicopathological variables in IHCC patients.

Methods: Thirty-one patients with IHCC who underwent hepatic resection were enrolled. Fbxw7 expression in tumor tissue was determined by immunohistochemistry and patients were divided into two groups, the Fbxw7 high expression group (n = 11) and the Fbxw7 low expression group (n = 20). We then compared clinicopathological variables including prognosis between the high and low expression groups in tumor tissue. In addition, the correlation between Fbxw7 expressions and cell proliferation, apoptosis and epithelial-mesenchymal transition (EMT).

Results: Fbxw7 expression was significantly correlated with staging (P = 0.006), and tended to correlate with lymph node metastasis. The Fbxw7 low expression group had significantly poorer prognosis compared with the Fbxw7 high expression group (P = 0.020); 3-year survival rates were 29.4% and 72.7%, respectively. Furthermore, the disease-free survival rate in the Fbxw7 low expression group was significantly worse than in the Fbxw7 high expression group (P = 0.022). On multivariate analysis, intrahepatic metastasis (P = 0.006) was a significant independent prognostic factor for disease-free survival, and Fbxw7 low expression tended to be an independent prognostic factor for both overall (P = 0.067) and disease-free survival (P = 0.083). The Fbxw7 low expression group had significantly correlated with the high expressions of Cyclin E1 and PCNA, with the low expressions of Caspase 3 and with the high expressions of MMP9 and Twist1.

Conclusion: Our results confirmed that low expression of FBXW7 in IHCC might correlate with tumor progression and poor prognosis in IHCC via regulating cell proliferation, apoptosis and EMT.

P2-57

T-Cell Factor-4 Isoforms Regulate Wnt5a Expression and EMT in Human Liver Cancer Cells

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Background: The T-cell factor (TCF)-4 is a key transcriptional protein activated by Wnt/ β -catenin signaling. Previously we identified 14 TCF-4 isoforms derived from human HCC cell lines (Exp Cell Res 2011). The TCF-4J and K pair have been characterized based on the presence (K) or absence (J) of a SxxSS motif. TCF-4J-overexpressing HCC cells (J cells) exhibited high tumorigenic potential in contrast to TCF-4K-overexpressing cells (K cells) (PLoS ONE 2012). However, K cells often showed morphological alteration, reminiscent of epithelial-mesenchymal transition (EMT), which is involved in non-canonical Wnt signaling (BMC Cancer 2013). The finding suggested that the SxxSS motif had potential to regulate EMT through the noncanonical Wnt signaling pathway. Thus, the AIM of this study was to investigate whether the SxxSS motif modulated expression levels of EMT regulators and Wnt5a, a representative non-canonical Wnt ligand.

Methods: The human HCC cell line HAK-1A (Hepatology 1993) was used. TCF-4K mutants (269A, 272A, and 273A) were prepared with conversion of serine (S) in the SxxSS motif to alanine (A) by site-directed mutagenesis. HAK-1A-derived stable clones overexpressing TCF-4J, K, and K-mutants (269A, 272A, and 273A cells, respectively) were established. Western blot analysis and real-time RT-PCR were employed to evaluate protein and mRNA expression levels, respectively. Sh-RNA was used to knockdown wnt5a gene expression.

Results: The 269A-mutant cells robustly expressed Wnt5a in both protein and mRNA levels, while empty vector-transfected cells (control), J cells, or K cells did not. Of note, Wnt5a expression was coupled with SLUG expression and EMT-like cellular morphological change. Snail was hardly expressed in the cells examined in this study. When the Wnt5a expression was specifically silenced by using sh-RNA, the expression level of SLUG was clearly decreased.

Conclusion: The findings in this study suggest that serine 269 (the first serine) of the SxxSS motif of TCF-4 is a major switch to control Wnt5a transcription, thereby modulating the expression level of the EMT-regulator SLUG in a human HCC cell line.

P2-58

PSPC1 Facilitates β -catenin Nuclear and Brk/PTK6 Cytoplasmic Translocations to Promote EMT and Metastasis of Hepatocellular Carcinoma

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Background: Metastasis, the dissemination and invasion of tumor cells from an originated organ to distant target tissue, is the most common cause of death in cancer patients. Progression of cancer cells to Epithelial-mesenchymal transition (EMT) has been associated with metastatic process. To further explore the molecular mechanisms and post-translational modification of PSPC1, we examined the crosstalk of PSPC1/ β -catenin/Brk (breast cancer kinase; PTK6) axis in EMT and metastasis of HCC.

Method: HCC clinical patient sample and three cell lines: SK-hep1, SNU-387, and Huh-7 were used in this study. Expression level of PSPC1, all forms of Brk, PSPC1 Y523F mutation and β -catenin was evaluated by Western blotting, immunofluorescence and immunohistochemistry. Endogenous PSPC1/ β -catenin complex on the TCF4/LEF1 promoter was assessed by TOP-Flash luciferase assay. The mouse orthotopic model of HCC was monitored by IVIS system.

Results: We found that PSPC1 is a kinase phosphorylation substrate of Brk through physical interaction in vivo and in vitro. Brk also sustained tumor suppressive activity to reduce PSPC1-mediated tumorigenic, EMT, CSC and metastatic features. When PSPC1 continued its aberrant overexpression in HCC or when the Brk phosphorylation site of PSPC1 (Tyrosine-523) was mutated (Y523F), PSPC1 increased Wnt1 expression through autocrine mechanism, deported Brk to cytoplasmic compartment to activate Brk oncogenic functions, and facilitated nuclear translocation of β -catenin to activate Wnt1/ β -catenin signaling pathway for promoting EMT, CSC and metastasis in HCC. Importantly, Y523F mutant of PSPC1 transfectant of HCC cells further enhanced EMT, migration and invasion features in cell models and increased lung metastasis in the mouse orthotopic model of HCC. When examined PSPC1, p-Brk and p-Y523 expression by HCC tissue arrays, we found that PSPC1 expression is negatively correlated with activated Brk expression and influenced survival ratio in metastatic HCC patient tissues.

Conclusion: our finding unravel a critical mechanism to explain the inhibitory effect and the interaction between

PSPC1 and Brk for modulating nuclear β -catenin translocation and activation of Wnt1/ β -catenin signaling pathway during EMT and metastasis of HCC.

P2-59

Verifying Absence of the Cytoskeleton in Nuclei of Liver Cells

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The structure of nuclei is supported by nucleoskeleton. Nucleoskeleton was proposed to be a critical and facilitating element in nuclear functions and play key roles in DNA replication. However, the nature of nucleoskeleton structure is still uncertain because of technical difficulties in its visualization. Cells of hepatocellular carcinoma are morphologically different from those of normal liver. Our previous studies indicated that plectin deficiency, via affecting the organization of cytoskeleton, might be an important issue in the pleomorphism of hepatocellular carcinoma cells. Although there are reports that plectin could pass through the nuclear pores to cross-link cytoplasmic intermediate filaments to lamin B (a component of nuclear envelope), it is quite plausible that plectin and cytoskeleton are also components of the nucleoskeleton. In this study, we are going to search whether the cytoskeletons are existent in the nuclei of liver cells by various techniques including nuclear isolation, Liu's stain, immunoblot analysis, immunohistochemistry and immunocytochemistry, immunofluorescence and confocal microscopy. The results revealed that by immunofluorescent staining using antibodies against cytokeratin18, actin and tubulin, we found all three compositions of cytoskeleton including intermediate filament, microfilament and microtubule are not existent in the nuclei of liver cells verifying by confocal microscopy. Conclusively, cytoskeletons are not existent in the nuclei of liver cells verifying by confocal microscopy. The immunohistochemically positive staining of plectin and cytoskeletal proteins in the nuclei, as well as the detection of these proteins in the nuclei by immunoblot, might be due to incomplete isolation of nuclei from the liver cells. We provide a simple and effective technique to evaluate the nucleoskeleton of liver cells and confirm the absence of cytoskeleton in the nuclei of liver cells. We also speculated that the events of pleomorphism in hepatoma cells might be prompted by modulation of cytoskeletons in cytoplasm.

P2-60

The Effects of HBx on the Expression of PUMA in HCC Cells and Its Mechanism

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Objective: To investigate the effects of HBx on the expression of PUMA in HCC cells and its mechanism.

Methods: Wild HBx plasmid was transfected into hepatocellular carcinoma cell line BEL-7402 and Huh-7. HBx mRNA expression was detected by RT-PCR, fluorogenic quantitative PCR and western blot were respectively administrated to the detection of NF κ B mRNA and proteins of HBx, p53, NF κ B and PUMA.

Result: The efficiency of transfection was about 25%~33%, and there was an expression peak of HBx mRNA 48 hours after transfection of HBx plasmid for BEL-7402 and Huh-7 cells. HBx induces the increase of mRNA and protein of NF κ B and reduces p53 protein in BEL-7402 and Huh-7 cell lines and PUMA protein is reduced simultaneously. But p53 and PUMA protein increases simultaneously following the inactivation of NF κ B by PDTC in BEL-7402 cell line. The HBx-mediated PUMA inhibition is not removed following the inactivation of NF κ B and the increase of p53 in Huh-7 cell lines.

Conclusion: These data show that HBx induces the inhibition of p53 via NF κ B signaling and that HBx-induced PUMA down-regulation is mediated not only through p53 dependent way but also through p53 independent way.

P2-61

Natural History of Dysplastic Nodules Detected During Surveillance for Hepatitis B Virus Associated Hepatocellular Carcinoma

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Background: Dysplastic nodule is a precancerous lesion which requires surveillance in patients with liver cirrhosis. Though confirmation of dysplastic nodule requires liver biopsy, most of the suspected dysplastic nodules are clinically diagnosed with contrast enhancement imaging modalities. However, the natural history of clinically suspected dysplastic nodules has not been well known yet. The aim of this study was to figure out the natural history of clinically suspected dysplastic nodules in patients with hepatitis B virus (HBV)-associated liver cirrhosis on surveillance for hepatocellular carcinoma (HCC).

Methods: For this retrospective cohort study, we examined consecutive HBV-associated liver cirrhosis patients who underwent more than 6 months of surveillance for HCC between May 2003 and December 2010. Diagnosis of liver cirrhosis was based on clinical, laboratory and imaging findings. Surveillance was done with ultrasound exam and AFP tests every 3–6 months. Diagnosis of dysplastic nodule was made when nodular lesion(s) showed portal hypo-perfusion without arterial enhancement on contrast-enhancement CT or MRI. The incidence of HCC was calculated by Kaplan-Meier analysis, and factors associated with increased HCC incidence were assessed by log rank test.

Results: A total of 624 HBV-associated liver cirrhosis patients were enrolled in this study. Among them, dysplastic nodules were found in 134 patients. The median duration of follow-up was 60 months. The incidences of HCC in these patients were 3%, 16%, 25%, and 38.8% in 1, 3, 5, and 7 years, respectively. The incidence of HCC was significantly higher in the patient group with elevated baseline AFP levels >10 ng/dl whereas age, albumin levels, platelet count or HBV DNA levels did not predict the risk of HCC.

Conclusions: This retrospective cohort study showed that 25% of clinically suspected dysplastic nodules progressed to HCC in 5 years, and that increased baseline AFP levels was associated with high risk for HCC in these patient group.

P2-62

Influence of Hepatitis B Virus DNA Elevation on Recurrence of Hepatocellular Carcinoma After Surgical Resection and the Preventive Role of Antiviral Therapy

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Background: Surgical resection is the treatment of choice for early stage hepatocellular carcinoma (HCC). Previous studies revealed that reactivation of hepatitis B virus is associated with the recurrence of hepatitis B virus (HBV) related HCC after surgical resection. We aimed to investigate the influence of HBV DNA elevation on HCC recurrence and the preventive role of antiviral therapy.

Methods: One hundred eleven patients who had BCLC stage 0 or A and received surgical resection as primary therapy were enrolled. HBV DNA elevation was defined as reactivation (increase >1log₁₀ IU/ml or re-emergence of HBV DNA) in patients without preoperative antiviral therapy or virologic breakthrough in patients with preoperative antiviral therapy (n = 62).

Results: Mean age was 54.1 ± 9.4 years and male consisted 76.6% (n = 85). All patients belonged in Child class A. BCLC 0 consisted 29.7% (n = 33) and 30.6% (n = 34) had Hepatitis B envelope antigen positivity and 42.3% (n = 47) had HBV DNA level ≥2000 IU/ml at the time of surgery. Overall 1 year, 3 year, 5 year recurrence was 17.3%, 36.4%, 40%. In multivariate analysis for risk factors of recurrence, multiple tumor, HBV DNA elevation, ALT ≥30 IU/L, were independently associated with HCC recurrence. In subgroup analysis, patients with preoperative antiviral therapy showed similar HCC recurrence rate with patients who start antiviral therapy after resection and significantly higher recurrence rate than patients with no antivirals during follow up. In multivariate analysis for risk factors of HBV DNA elevation, Age <50 years, no preoperative antiviral therapy, HBV DNA ≥2000 remained as risk factors. To rule out the antiviral effect, we investigated risk factors for HCC recurrence in each group with or without preoperative antiviral therapy. In patients with preoperative antiviral therapy, multiple tumor was the only risk factor for HCC recurrence. In patients without preoperative antiviral therapy, male sex and HBV DNA elevation were independent risk factors for HCC recurrence. Risk factors for HBV DNA elevation were further analyzed in patients without preoperative antiviral therapy. Age <50 years and HBV DNA ≥2000 IU/ml were independent risk factors for HBV DNA elevation.

Conclusion: HBV DNA elevation after resection increases the risk of HCC recurrence irrespective of preoperative antiviral therapy. However, HBV DNA elevation is an independent risk factor for recurrence in patients without preoperative antiviral therapy. Therefore, perioperative antiviral therapy should be considered to prevent HBV DNA elevation and recurrence, especially in patients with Age <50 years and/or HBV DNA ≥2000 IU/ml.

P2-63

Association of HBV DNA Level & Antiviral Agent on the Recurrence of Patients After Liver Resection for Hepatitis B Virus-Related Hepatocellular Carcinoma

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Background: Hepatitis B virus (HBV) levels correlate with the development of hepatocellular carcinoma (HCC), but the role of viral load and treatment in HCC recurrence after tumor resection remains unclear. Herein we aimed to investigate the significance of HBV DNA levels & antiviral agent for predicting recurrence in HCC patients who underwent curative liver resection.

Methods: From 2005 to 2010, 341 HBV-related HCC patients who underwent tumor resection in SNUH were enrolled. HBV DNA levels (pre-, postop. period) & antiviral treatment were analyzed for association with HCC recurrence, together with other clinical variables.

Results: Of the 294 patients, patients (n = 164) with low postop. HBV DNA (1×10^3 IU) had better outcome than those (n = 130) with high load in recurrence (5 yr-Recurrence free survival (RFS) = 43.2 vs. 22.2%, $p < 0.001$). In terms of Antiviral agents, untreatment group (n = 136) had worse outcome than treatment group (n = 158) in recurrence (5 yr-RFS = 28.3 vs. 56.3%, $p < 0.001$). In subgroup analysis, if the treatment group had high HBV viremia postoperatively, they had good RFS as group with low viremia (5 yr-RFS = 54.1 vs. 58.3%). But, even if untreated patients had low viremia, they had poor outcomes as untreatment group with high viremia (5-yr RFS = 37.1 vs. 11.9%). Moreover, whether it is advanced stage (3) or not, low postop. HBV load showed the better recurrence outcome but, antiviral treatment did not present difference in advanced stage. Finally, postop AFP levels as well as postop HBV DNA antiviral therapy, tumor size, microvascular invasion were independent risk factors for RFS in multivariate analysis.

Conclusions: Low HBV DNA load and antiviral therapy may be important factors after the curative treatment of HBV-related HCC in terms of tumour recurrence. Therefore, to maintain the low level of HBV viremia, antiviral therapy should be considered after curative treatment of HCC.

levels may increase without HCC, leading to impaired specificity of AFP. However, quantitative relationship between HBV DNA titer and AFP level is not well known. This study aimed at analyzing the factors, besides HCC, that may increase AFP level in patients with chronic HBV infection, with special focus on the effect of HBV viral load.

Methods: Chronic hepatitis B (CHB) patients who underwent surveillance for HCC in Seoul National University Bundang Hospital between 2003 and 2015 were eligible for this study. Patients with previous diagnosis of HCC or with subsequent detection of HCC during surveillance were excluded from the analysis. Data of the patients were extracted from the electronic medical record-based data warehouse. Biochemical, serological, and virological data were analyzed by multiple regression analysis in order to find potential correlation with AFP levels.

Results: A total of 6564 patients were enrolled in this study. Median duration of follow up was 26.4 months. Median AFP level at the end of follow up were 2.3 ng/ml (range, 0.1–40000), and 6.0% of patients showed >20 ng/ml. Multiple logistic regression analysis revealed that platelet count and albumin levels negatively affected AFP levels, whereas ALT, GGT, bilirubin, monocyte count and HBV DNA titer were independent parameters that positively affected AFP levels.

Conclusions: In addition to biochemical and hematologic parameters, HBV DNA titer was an independent factor which may spuriously increase AFP levels in CHB patients. HBV viral load should be considered in assessing AFP levels for HCC surveillance.

P2-64

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Hepatitis B Virus Viral Load Positively Affects Serum Alpha-Fetoprotein Levels in Chronic Hepatitis-B Virus Infection Without Hepatocellular Carcinoma

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Background: Alpha fetoprotein (AFP) is the most widely used biomarker for hepatocellular carcinoma (HCC) surveillance. In chronic hepatitis-B virus (HBV) infection, serum AFP

P2-67

Risk Factors for Developing Liver Cancer in Patients Undergoing Entecavir Therapy for Chronic Hepatitis B Virus-Related Liver Disease

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Objective: Treatment outcomes of patients with chronic hepatitis B virus (HBV)-related liver disease have improved since the advent of nucleoside/nucleotide analogues (NAs), but there are still cases in which cancer of the liver develops despite sufficient therapeutic responses to treatment with NAs. We investigated the present status of patients with chronic HBV-related liver disease receiving entecavir (ETV) and the characteristics of those in whom liver cancer developed despite this treatment.

Patients and Methods: Of 534 patients with HBV-related liver disease treated at our hospital, 90 patients with chronic HBV-related liver disease who had received ETV for at least 1 year without a history of hepatocellular carcinoma (HCC) at

Table 1. Independent risk factors related to HCC-IDR: multivariate analysis (for Abstract P2-68)

	SE	χ-squared	Hazard ratio	95% CI	P value
Pretreatment A1b <3.5 g/dl	1.239	4.587	14.19	1252–160.179	0.032
Multinodular tumor	1.397	6.349	0.03	0.002–0.457	0.012
No or disrupted periablation enhancement within 24 hours of REA	1.177	10.132	0.024	0.002–0.237	0.001
T1-hyperintensity of the central ablative zone at 1 month after RFA	1.381	9.123	64.88	4.327–972.774	0.003

HCC = Hepatocellular carcinoma; IDR = intrahepatic distant recurrence; SE = standard error; CI = confidence interval; Alb = albumin; RFA = radiofrequency ablation.

the start of ETV therapy and who had been followed with regular checkups (median age at start of ETV therapy, 52 years [28–84]; and mean observation period, 1721 days) were reviewed and analyzed to explore risks for developing liver cancer.

Results: The HBV-DNA level was reduced to <2.1 log copies/ml in 79.7% of the patients at 6 months and in 94.5% at 1 year after starting ETV treatment. As for serum ALT levels over time after the start of ETV therapy, this hepatic enzyme level was 151 ± 182 at baseline, 27.1 ± 16.3 at 6 months, and 24.1 ± 17.2 (IU/ml) at 1 year of ETV therapy; thus, a significant decrease was documented with this treatment. Platelet counts over time were 14.8 ± 5.8 at baseline, 15.0 ± 5.9 at 1 year, and 15.6 ± 4.8 ($\times 10^4/\mu\text{l}$) at 3 years of ETV therapy, showing no appreciable decrease. Among the 90 patients studied, there were 5 patients (5.5%) found to have HCC after the start of ETV therapy. When compared with cancer-free patients ($n = 85$), those in the liver cancer group ($n = 5$) were older ($p = 0.024$) and showed lower platelet counts ($p = 0.05$) at baseline. More specifically, two of the patients who developed liver cancer had a platelet count of $\leq 5 \times 10^4/\text{ml}$ and two others in whom histopathological stage was $\geq \text{F3}$ had a platelet count of $\geq 10 \times 10^4/\text{ml}$ at the baseline.

Conclusion: The present results demonstrate that long-term treatment with ETV led to quiescence of hepatitis and suppression of disease progression to fibrosis; however, a higher risk for developing liver cancer in elderly patients and those with progressive fibrosis was revealed, even after the start of ETV therapy, stressing the importance of appropriately judging the optimal timing for treatment initiation.

P2-68

Risk Factors for Intrahepatic Distant Recurrence Following Complete Radiofrequency Ablation for Hepatitis B-Related Small Hepatocellular Carcinoma (≤ 3 cm): An Early Evaluation with MRI

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Backgrounds: Radiofrequency ablation (RFA) is related to a high intrahepatic distant recurrence (IDR) rate, and the associations between IDR and relevant imaging features have not yet been fully explored. We aimed to determine both clinical and imaging risk factors of IDR following complete RFA for hepatitis B-related small hepatocellular carcinoma (HCC) (≤ 3 cm).

Methods: Thirty-five patients (29 men and 6 women; mean age, 60.7 years) with 40 hepatitis B-related small HCCs who underwent complete RFA were included in our study. The incidence and potential clinical and MR imaging risk factors for IDR following RFA were assessed using the Kaplan-Meier method, the log-rank test and a stepwise Cox hazard model.

Results: The median follow-up period was 25 (4–45) months, and IDR was observed in 20 (57.1%) patients. The 12- and 24-month cumulative IDR-free survival rates were 76.7% and 61.3%, respectively. Univariate analysis revealed that pretreatment albumin <3.5 g/dl ($P = 0.026$), multinodular tumor ($P = 0.032$), ablative margin <3 mm ($P = 0.007$), no or disrupted periablation enhancement within 24 hours ($P = 0.001$) and at 1 month ($P = 0.043$) after RFA and hyperintensity of the central ablative zone on T1 weighted images (T1WI) at

1 month after RFA ($P = 0.004$) were related to IDR. Multivariate analysis revealed that pretreatment albumin <3.5 g/dl ($P = 0.032$), multinodular tumor ($P = 0.012$), no or disrupted periabdominal enhancement within 24 hours of RFA ($P = 0.001$) and hyperintensity of the central ablative zone on T1WI at 1 month after RFA ($P = 0.003$) were independent risk factors for IDR. During the 1-month follow-up, the apparent diffusion coefficient exhibited an up-and-down evolution without significant value in the prediction of IDR following RFA.

Conclusion: Hepatitis B-related patients with low serum albumin, multiple nodules, and lesions with no or disrupted periabdominal enhancement and persistent hyperintensity in the central ablative zone on T1WI within the 1-month follow-up after RFA have a higher risk of IDR.

P2-69

Hepatocellular Adenoma Treated with Percutaneous Radiofrequency Ablation: A Case Report

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A 32-year-old woman was found to have a liver tumor of 3 cm in diameter in segment 4/8 when she underwent medical checkup in November, 2010. Because CT and MRI failed to give sufficient information for the diagnosis, she underwent liver tumor biopsy at another hospital, which confirmed the diagnosis of hepatocellular adenoma (HA) in April, 2011. She did not have any particular medical history or medicines. Hypervascularity of the tumor had gradually become more evident while the tumor size had not increased. Surgical resection was recommended. However, she chose radiofrequency ablation (RFA) and visited our hospital. RFA was performed using cool-tip RF needle (COVIDIEN). CT scan after RFA showed entire tumor necrosis in January, 2013. No complications related to the procedure occurred. Follow-up EOB-MRI and blood test were performed every four months. MRI showed a reduction in tumor size with no abnormal enhancement or other evidence of recurrence. HA is a rare benign tumor occurring primarily in young women. HA is associated with use of oral contraceptives, anabolic androgens, and glycogen storage disease. In women using contraceptives in long term, the estimated annual incidence is 30–40 per 1,000,000 per year while in women not using contraceptives, the estimated annual incidence is 1 per 1,000,000 per year. HA has risk of rupture and malignant transformation. Therefore, operation is recommended for treatment of HA. Asymptomatic patients with small lesions (<5 cm) are advocated a conservative approach with close observation of the lesion

with repeated imaging and AFP determination. On the other hand, if the presumed adenoma has grown in size after 6 months of follow up, surgical resection is recommended. Although surgical resection is a generally recommended treatment for large or symptomatic HA, RFA may be a treatment of choice in selected patients.

P2-70

A Case of Hepatic Angiomyolipoma Which Had Difficulty in Differentiation with the Hepatocellular Carcinoma

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Background: In general, angiomyolipoma (AML) of the liver is well-known and is considered as benign, but preoperative diagnosis of images is sometimes difficult because of its ratio variety among the three basic components. Especially epithelioid type of AML (PEComa) is difficult in clinical diagnosis. We report a unique case of AML in images and pathological findings.

Case Report: A 63 year old woman was pointed liver tumor (35 mm in segment 4,) by abdominal ultrasonography. Both of HBs antigen and HCV antibody were negative and tumor markers were also negative and each enzyme of hepatic-cystic system was all within normal range. Dynamic computed tomography (CT) imaging revealed that homogeneous enhancement in the early arterial phase and showed irregular enhancement areas and iso-density with liver parenchyma in portal and delayed phase. The magnetic resonance imaging (MRI) findings of these tumors revealed a light high-intensity on T2 weighted images and low-intensity on T1 image in almost the tumor. There was a slightly difference of intensity in In-Out phase especially in out layer of the tumor, which suggested the component of the fat. Dynamic MRI imaging revealed that high intensity in early phase and ring-shaped prolonged enhancement in hepatobiliary phase. In contrast enhanced ultrasonography revealed that hyper vascular in whole area of the tumor in arterial phase and defect in Kupffer phase inner area of the tumor. We supposed it hepatocellular carcinoma or benign tumor with hyper vascularity, and hepatectomy was performed.

Results: Macroscopically, it had two-layer structure. Pathologically, inner area of the tumor were diagnosed as angiomyolipoma (AML) with positive reaction for melanocytic (Melan A, HMB-45) and smooth muscle (SMA) markers immunohistochemically. But the outer layer of the tumor revealed negative reaction for Melan A, HMB-45 and SMA but

positive reaction for glutamine synthetase (GS) and Hep-per1 and contained fat component.

Conclusion: We found a unique case of AML wearing zonal hyperplastic change of hepatocytes induced by drainage hyper-blood flow that had difficulty in diagnosis before the operation.

P2-71

An Examination of Three Cases of Hepatic Metastasis That Developed After Pancreaticoduodenectomy for Pancreatic Carcinoma and Was Treated with Radiofrequency Ablation

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Radiofrequency ablation (RFA) after choledochojunctionostomy is contraindicated because of a high risk of developing postoperative liver abscesses. In this study, we examined cases of RFA-treated hepatic metastasis that developed after pylorus-preserving pancreaticoduodenectomy (PpPD) for cancer of the head of the pancreas. Fully informed consent was obtained from all patients. We examined 3 cases of solitary metastasis without pneumobilia in the ablated bile duct. For RFA, the current was applied with a 2-cm cooled-tip electrode needle (Covidien) until 3 voltage peaks were observed. Antibiotic therapy was initiated the day before RFA and maintained for a week after the procedure.

Case 1: A woman in her 70 s, who had undergone a right nephrectomy for cancer of the right renal pelvis and parenchyma in 1986, underwent a PpPD and resection of the right half of the colon for cancer of the head of the pancreas in May 2012. The pancreatic margin was positive, and she received TS-1 treatment after the surgery. A hepatic metastasis, 15 mm in diameter, in segment 5 was detected by computed tomography (CT) in April 2013, and retention of pericardial fluid and ascites was observed. RFA was performed on May 15, 2013. After RFA, no adverse events or local recurrences developed. The patient experienced progressive cardiac and renal failure in December 2013 and died in June 2014.

Case 2: A woman in her 60 s underwent PpPD for cancer of the head of the pancreas in June 2013. After the surgery, she was treated with TS-1. A hepatic metastatic lesion with a diameter of 12 mm in segment 7 (S7) was detected by CT in December 2013. RFA was performed on January 9, 2014, and no adverse events or local recurrences developed after the surgery; TS-1 treatment was maintained. In March 2015, ethoxybenzyl-magnetic resonance imaging (EOB-MRI) revealed no intra- or extrahepatic recurrences, and TS-1 treatment was discontinued.

Case 3: A man in his 60 s underwent PpPD and portal vein resection for cancer of the head of the pancreas in May 2014. After the surgery, he received gemcitabine and TS-1 treatment. In February 2015, EOB-MRI showed a hepatic metastasis with a diameter of 10 mm in S7. RFA was performed on March 11, 2015, and no adverse events developed after the surgery. Pancreatic carcinoma with hepatic metastasis has a poor prognosis; however, we experienced cases in which local therapy for late postoperative hepatic metastases clearly improved the prognoses. It has been suggested that RFA be considered one of the multidisciplinary approaches for treating certain cases of hepatic metastases from pancreatic carcinoma that develop after PpPD.

P2-72

A Case of Lymph Node Metastasis of HCC Effectively Cured by Cyberknife

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Background: Although the treatment algorithm of HCC has been well documented in Japan, it shows limited options for patients with extrahepatic metastasis. Sorafenib, the only approved drug for systemic chemotherapy, is recommended to use only for patients with better liver function, i.e. Child-Pugh (CP) grade A. CyberKnife® (CK), a stereotactic body radiotherapy, has no major adverse effects and recently applied to various cancer including liver. The indication of CK for HCC has not been established despite reports of efficacy. Here, we present a case treated by CK for obvious lymph node metastasis whose primary HCC was controlled.

Case: A case is 68 year-old male. He was treated by interferon for hepatitis C at age 60, and achieved sustained viral response. Poorly differentiated HCC was identified and hepatectomy (S4/8) was performed in 2011. One year later, lymph node metastasis (#12, #13) was detected by CT, while no recurrence or new lesion was found in the liver. He desired less-invasive therapies and received CK by total 54 Gy. Although each size was 39×34×76 mm and 30×32×80 mm at the start of treatment, these lymph node shrunk and became disappeared lasting for 2 years.

Discussion: This case might be recommended to take sorafenib according to the present guideline because of CP grade A and the existence of extrahepatic lesions. Although sorafenib is widely recognized to prolong overall survival in HCC beyond the indication of loco-regional treatments, it often causes severe adverse effects, e.g. hand-foot syndrome, and may affect liver function, therefore having the limitation to use only for CP grade A. On the other hand, CK is much less

invasive to any area other than the focused lesion and may be applied to all HCC patients regardless of liver function. However, due to the shortage of evidences and definite reports, CK is not set as the first line treatment of primary HCC compared to hepatic resection, RFA and TACE. Though still challenging for extrahepatic lesions, as shown in our patient, CK is much effective to lymph node metastasis and may prolong survival, at least, if primary lesion is controlled.

Conclusion: CK should be considered as a treatment option for patients with lymph node metastasis whose primary HCC is controlled.

P2-73

A Case of Multiple Focal Nodular Hyperplasia with Donut-Like High Intensity on Hepatobiliary Phase of Gd-EOB-DTPA Enhanced MRI

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We report a case with multiple focal nodular hyperplasia with donut-like high intensity on hepatobiliary phase of Gadoxetate (Gd-EOB-DTPA)-enhanced MRI. A 24-year-old woman was introduced to our hospital for further examination of liver

dysfunction in May 2008. She had taken low-dose pill for menstrual irregularity from May to October, 2007. A physical examination on admission showed no remarkable abnormalities except for conjunctival icterus. The levels of hepatic tumor markers, α -fetoprotein and des- γ -carboxyprothrombin, were within normal limit, and anti-hepatitis C virus antibody and hepatitis B surface (HBs) antigen were negative. On abdominal ultrasound, multiple iso- to slightly hyperechoic nodules less than 25 mm in diameter were detected and contrast enhanced US showed centrifugal enhancement of the nodule. These nodules showed isodensity in non-contrasted CT and showed hypervascularity in the early phase of dynamic CT. The center of the nodule showed no enhancement. These lesions showed slightly high intensity with low intense center in pre-contrasted phase, high intensity in the arterial phase, iso intensity in the equilibrium phase, and peripheral donut-like high intensity of the lesion in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. Based on these findings, we diagnosed these nodules as multiple focal nodular hyperplasia (FNH) accompanied with central scar. However, because of the increase of tumor size after 7 months: 18 mm to 23 mm and 25 mm to 30 mm in diameter in segment 1 and 2, respectively, in MRI, the hepatic resection was performed for these nodules. Resected specimen showed the well-demarcated nodules with central scars and were diagnosed as FNH. Immunohistochemistry showed strong positive expression of glutamine synthetase (GS) in the peripheral areas of the nodule, whereas organic anion transporter 8 (OATP8) and multidrug resistance-associated protein 3 (MRP3) were equally expressed in the nodule. Signal intensity in hepatobiliary phase of EOB-MRI usually seems to correspond to the expression of OATP8. In this case, however, high signal intensity seemed to correspond to the expression of GS, not to that of OATP8.