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Advancing HCC Management through
Multi-Disciplinary Approach

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Abstracts

Guest Editor

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Speaker's Lecture Abstracts

Session 1: State-of-the Art Lecture

Recent Advancement in HCC Treatment

8 July 2016 (Friday), 08:30–09:00

Masatoshi Kudo

Professor and Chairman, Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Japan

Recent Advancement in HCC Treatment

I. Heterogeneity of Intermediate Stage HCC

There is big heterogeneity in the intermediate stage HCC. Usually, TACE is performed in patients with multiple tumors, no vascular invasion and no extrahepatic spread. However, in Japan the nodules are fewer and smaller compared to Western countries and the other Asian countries, where tumors are larger or multilobar nodules. Therefore, intermediate stage HCCs should be subclassified in order to select the optimal treatment option.

II. New Trends of TACE Procedure

Until now, the standard technique of TACE in Japan was superselective TACE using Lipiodol and gelatin sponge because of the fewer and smaller nodules in the liver. However, microsphere such as DC Beads or hepasphere was approved to use. In addition, balloon occluded TACE (B-TACE) was developed to achieve dense accumulation of anticancer agent. Optimal indication for each technique, i.e., conventional Lip TACE, DEB TACE or B-TACE should be determined in the near future.

III. Definition of TACE Failure

Definition of TACE failure proposed by Japan Society of Hepatology is as follows:

Definition of TACE Failure/Refractoriness (JSH)

(1) Intrahepatic lesion

i Two or more consecutive insufficient responses of the treated tumor (viable lesion >50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE.

ii Two or more consecutive progressions in the liver (tumor number increases as compared to tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE.

(2) Continuous elevation of tumor markers immediately after TACE even though slight transient decrease is observed

(3) Appearance of vascular invasion

(4) Appearance of extrahepatic spread

Two validation studies were conducted and proved that this definition is adequate.

IV. Molecular Targeted Therapy: Current Status and Future Perspective

Sorafenib is the only targeted agent that was proved to prolong the survival of the patients with advanced HCCs. During 7 years since its approval, 13 global studies that tested 1st line, 2nd line, TACE combination, and adjuvant setting after curative treatment failed. SILIUS trail that tested the survival benefit of hepatic arterial infusion chemotherapy plus sorafenib also failed. However, regorafenib after sorfenib failure as a second line treatment was proved to be an effective agent, that prolongs survival in patients with advanced HCC. Regorafenib will change the treatment paradigm in HCCs.

Session 2: Basic Science

Orchestration of HCC Development by Diverse Liver Cancer Stem Cells

8 July 2016 (Friday), 09:00–09:20

Xin-Wei Wang

Chief of Liver Carcinogenesis Section, Deputy Chief of Laboratory of Human Carcinogenesis, Senior Investigator, Center for Cancer Research, National Cancer Institute, USA

Hepatocellular carcinoma (HCC) is the second most lethal cancer in the world and is extremely heterogeneous in terms of its etiological factors, tumor genomics and biology. Tumor heterogeneity may emanate from the presence of cancer stem cells (CSC) and selection by clonal evolution. Various etiological factors may elicit different molecular mechanisms on progenitor cells to induce HCC. Consequently, HCC is genomically heterogeneous and consists of many molecularly distinct subtypes, which poses a significant challenge to cancer management. Several hepatic stem/progenitor cell surface markers such as CD13, CD24, CD44, CD90, CD133, EpCAM and OV6, have been shown to be useful for isolating a subset of cancer initiating cells with stem-cell features. These cells are responsible for tumor relapse, metastasis, and chemoresistance. Liver CSCs dictate a hierarchical organization that is shared in both organogenesis and tumorigenesis. However, liver CSCs are also heterogeneous in marker expression, which may be responsible for both intra- and inter-tumor heterogeneity. Although therapies that target CSCs hold promise in eliminating cancer burden, normal stem cells are likely to be targeted due to their similarities with CSCs. To tackle these issues, molecular-based technologies including genomic, transcriptomic and metabolomic profiling, have been used to distinguish CSC-related tumor subgroups, which allow for stratification of patients with greater homogeneity and can assist in molecular re-staging. These various genome-based signatures also delineate critical gatekeepers of cancer initiation and progression, which can be further honed by integrated genomics to identify key driver genes and functionally linked networks in HCC. In addition, identification of specific molecular events distinguishing CSCs from normal stem/progenitor cells is essential towards developing effective molecularly targeted therapy. An increased understanding of the molecular signaling events that regulate cellular hierarchy and stemness, and success in defining key CSC-specific genes, have opened up new avenues to accelerate the development of novel diagnostic and treatment strategies.

Molecular Pathogenesis of HCC Beyond the Antiviral Therapy

8 July 2016 (Friday), 09:20–09:40

Shiou-Hwei Yeh

Distinguished Professor, Department of Microbiology, National Taiwan University College of Medicine, Taiwan

Hepatocellular carcinoma (HCC), the fifth most common solid malignancy, accounts for approximately three-quarter of a million deaths every year worldwide. Chronic infections with HBV or HCV are the major risk factors for HCC, being associated with more than 80% of cases. According to the drastic advances in the development of oral direct-acting antivirals (DAA), their impact on reducing the tumorigenesis of chronic hepatitis (CH) patients has been studied. DAA treatment can effectively suppress the viral replication in CH patients, even with prolonged SVR, which however only reduce the tumor incidence but not eliminate the risk of HCC. The predictors for HCC developed in DAA treated patients include the male gender, older age, more advanced liver diseases, and some others. New therapeutic regimens need to be developed for intervening the carcinogenic process in these patients, via targeting to the specific mechanisms critical for their tumorigenesis. An increasing genetic/epigenetic changes and signaling pathways have recently been delineated in HCC by next generation sequencing analysis. Allocating these events in the subgroup of HCC developed after curative DAA therapy can help guide specific therapeutic regimens. Moreover, as noted that the male gender is one of the major predictors for this subgroup of HCC, we have examined the involvement of the male specific androgen pathway in liver carcinogenesis. Using the HBx transgenic mouse model, we found that the tumor incidence was significantly decreased by knockout of hepatic AR or by castration at early ages. This pathway could thus be a druggable target for the chemoprevention of HBV-related HCC, through activating the liver enriched SHP-1 phosphatase. The results provides a novel target with great potential for development of a tissue- and disease-specific regimen to prevent HCC in male CHB patients. Its effect for preventing HCC in DAA treated CH patients is worthy to be investigated.

HCC Molecular Features and Potential Targeted Therapeutics

8 July 2016 (Friday), 09:40–10:00

Siu-Tim Cheung

Associate Professor, Department of Surgery, The Chinese University of Hong Kong, Hong Kong

Hepatocellular carcinoma (HCC) is a major cause of cancer death in China and worldwide. Curative treatments including surgical resection and transplantation are applicable only for early-stage patients. The majority of HCC patients are diagnosed at an advanced stage because of limited surveillance and that early-stage HCC is usually asymptomatic. Treatment options for advanced-stage patients are limited and systemic chemotherapies have dismal response rates. Sorafenib, a multi-kinase inhibitor, has demonstrated survival benefits of approximately three months in advanced HCC patients. Known with limited effectiveness, nonetheless, adjuvant sorafenib had no effect on the prevention of HCC recurrence. Extensive molecular efforts have revealed the key pathways and drivers in HCC development and progression. Altered signaling including growth and angiogenesis (EGF, FGF, GEP, HGF, IGF, PDGF, VEGF), differentiation and cancer stem cell axis (WNT/beta-catenin, Hedgehog, Notch, TGF-beta) and signaling mediator (ras/raf/mek/erk, PI3K/Akt/mTOR). Targeted therapeutics including monoclonal antibody, inhibitor and immunotherapy will be deliberated. Research effort should continue to further exploit the molecular markers to stratify patients based on prognosis and response to therapeutics.

Session 3: State-of-the Art Lecture

Immunotherapy for HCC

8 July 2016 (Friday), 10:10–10:35

Bruno Sangro

Director, Liver Unit, Clinica Universidad de Navarra, Spain

Several approaches to enhance the immune response against tumor cells have failed to provide treatment benefit in advanced hepatocellular carcinoma (HCC) including dendritic cell vaccination, cytokine-induced killer cells or oncolytic viruses expressing immunostimulating cytokines. Following the proof of concept in melanoma patients, it has been shown that T-cell checkpoint modulation may break the barrier that different tumor types create to evade the attack from the immune system.

In fact, enhancing T cell function by targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) using monoclonal antibodies has revolutionized the field of cancer immunotherapy. Tremelimumab (anti-CTLA-4) has provided the first signal of activity and favorable safety profile in a phase II clinical trial targeting HCC patients with chronic HCV infection. In a small group of 21 patients, Tremelimumab produced an overall response rate of 18% while 59% of patients had a stable disease that in almost half of the cases lasted for more than 6 months. A median time to progression of 6.5 months provided further evidence of anti-tumor activity. These results paved the way for other checkpoint inhibitors.

Nivolumab (anti-PD-1) has very recently provided strong signal of anti-tumor activity in a phase I/II clinical trial. A dose-escalation cohort was followed by a large expansion cohort, and uninfected patients as well as patients with chronic HCV infection or chronic HBV infection under control by antiviral agents were recruited worldwide. Altogether, a large population of nearly 250 patients with fairly advanced HCC has been treated, most of them already exposed to Sorafenib. Following Nivolumab, 15% of patients reached an objective tumor remission (including several complete responses) and an additional 50% had stable disease that was frequently durable. Regarding survival, a 9-month survival rate of 70% was reported in the large expansion cohort while a median overall survival of 14 months (irrespective of prior Sorafenib treatment) was reported in the dose-escalation cohort with a longer follow-up. Importantly, these results were obtained with only a 1% rate of intense (CTCAE grade ≥ 3) symptomatic adverse events. Other checkpoint inhibitors have started clinical development and, following reports of synergistic effects in melanoma, a lot of interest is focused on combinations. CTLA-4 plus PD-1 or PDL-1 blockade is being explored in 2 different trials using the combination of Ipilimumab plus Nivolumab or Tremelimumab plus Durvalumab, and their results are eagerly awaited.

Session 4: State-of-the Art Lecture

Surgical Treatment of HCC: What is the Limit?

8 July 2016 (Friday), 11:10–11:40

Ronnie Poon

Honorary Clinical Professor, Department of Surgery, The University of Hong Kong, Hong Kong

Surgical resection is the mainstay of curative treatment for HCC. However, the resection rate of HCC remains low. Most patients with HCC has underlying cirrhosis with limited liver function reserve, which may make resection impossible even for early HCC. Furthermore, in most Asia-Pacific countries, the majority of patients present with advanced tumors which may not be considered suitable for resection. In recent years, safety of hepatic resection has improved due to advancement in surgical technologies and perioperative care. As a result, surgical indication of HCC has been expanded.

Improved assessment of liver function reserve including special liver function test such as indocyanine green test and liver volumetry has allowed more refined selection of patients. For patient with inadequate liver remnant volume, portal vein embolization has allowed resection in some patients with successful hypertrophy of future liver remnant. ALPPS (Associating liver partition and portal vein ligation) for staged hepatectomy has been developed as an alternative surgical strategy for patients with inadequate liver remnant volume.

The advent of ablation has allowed combined resection and ablation for patients with bilobar multifocal tumors. Improved techniques of vascular reconstruction have allowed resection of HCC encasing major intrahepatic or extrahepatic vessels. While portal vein invasion is considered a contraindication of resection in some HCC treatment algorithms, data from our centers and others have showed that reasonable long-term survival results could be achieved in selected patients with tumor invasion into intrahepatic portal vein or even main portal vein. In selected patients with isolated extrahepatic metastasis, resection may also provide long-term survival.

Recent development of liver surgery has allowed expanded role in treatment of HCC for some patients, including patients with more advanced tumors. To further expand indication of resection, effective nonsurgical therapies need to be developed to allow downstaging of advanced HCC to surgical resection, which is the main treatment modality providing a chance of cure.

Session 5: Systemic Therapy

Highlights on Targeted Therapy for HCC

8 July 2016 (Friday), 11:40–11:55

Richard S. Finn

Associate Professor of Medicine, Division of Hematology/ Oncology,
Geffen School of Medicine, University of California, USA

For almost a decade the multi-targeted kinase inhibitor sorafenib has been the only agent that has been proven to improve survival in advanced HCC. Since its initial approval in 2008, there have been numerous failures in both the front-line and second-line advanced disease setting, as well as in intermediate and the adjuvant setting. We can hypothesize the negative studies were driven by both failure of the 'drug' characteristics and failure of clinical trial design. Only recently, did we hear about the positive results from the randomized, placebo controlled, Phase III RESOURCE trial in HCC, evaluating the multi-kinase inhibitor regorafenib. These results are a first in the second-line setting and will change the treatment landscape for advanced HCC. While most important for patients, it is further evidence that we can improve outcomes beyond sorafenib. Still, we have seen other data of recent that has generated significant excitement in HCC. These include early data with immunotherapy agents directed at the PD-1 pathway. In addition, there are still promising data evolving with agents targeting other signal transduction pathways. We will review these data in the presentation.

The Roles of Chemotherapy for HCC

8 July 2016 (Friday), 11:55–12:10

*Chiun Hsu*Professor, Department of Oncology, National Taiwan University
Hospital, Taiwan

The roles of cytotoxic chemotherapy for HCC have been controversial because of the variable efficacy data reported in previous clinical trials and the concerns of treatment-related adverse events. In the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014), experts in Asia Pacific areas sought to develop consensus regarding the design of future clinical trials of systemic cytotoxic chemotherapy for advanced HCC, including the target population (second-line vs. first-line), inclusion criteria, treatment regimens, and trial endpoints. However, in the past 2 years the landscape of drug development for advanced HCC has changed a lot. In this presentation the current status of cytotoxic chemotherapy will be summarized and perspectives of future development will be discussed.

Systemic Therapy for Cholangiocarcinoma

8 July 2016 (Friday), 12:10–12:25

Andrew X. Zhu

Director, Liver Cancer Research, Massachusetts General Hospital Cancer Center, USA

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. Novel genetic signatures including IDH mutations and FGFR2 fusions have been identified in ICC and early clinical trials targeting these unique signatures are underway. The author will discuss the current status of systemic therapy in cholangiocarcinoma.

Session 6: State-of-the Art Lecture

Evolution of Liver Transplant for HCC

8 July 2016 (Friday), 14:00-14:30

Chung-Mau Lo

Head, Department of Surgery, The University of Hong Kong, Hong Kong

Will be presented at the meeting.

Session 7: Loco-Regional Therapy

Y90 Radioembolization for HCC

8 July 2016 (Friday), 14:30–14:45

Riad Salem

Professor, Department of Radiology, Feinberg School of Medicine,
Northwestern University, USA

Treatment options for liver tumors that cannot be resected are based on trans-arterial techniques. Y90 microspheres represents one of those trans-arterial options. During the past 15 years, numerous studies involving larger cohorts, comparative effectiveness and small randomized studies have provided evidence of the safety and efficacy of Y90 in HCC. The versatility of this therapy is also highlighted in with selective lobar/segmental infusion with the intent of preserving functional liver reserve, downstaging to resection, radiofrequency ablation or liver transplantation. Of recent significant interest are radiation segmentectomy and lobectomy, treatment options that challenge RFA and PVE in HCC. The role in portal vein thrombosis is also of significant clinical interest given the limited outcomes with sorafenib in this scenario. This presentation will review the state of the science and present role of radioembolization in HCC, as well as provide an update on the ongoing randomized phase 3 trials. Results from the PREMIERE trial, a randomized phase 2 trial comparing Y90 to cTACE with TTP as the endpoint, will also be presented.

Recent Advances in TACE for HCC

8 July 2016 (Friday), 14:45–15:00

Stephen L. Chan

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

Transarterial chemoembolization (TACE) has been used in the treatment of hepatocellular carcinoma (HCC) for more than 2 decades. Two randomized controlled trials have confirmed the role of TACE in patients with locally advanced or multifocal HCC. The optimal population and contra-indications to be benefited from TACE has also been clearer in the last decade. Generally, patients with vascular invasion or thrombosis in the main trunk of portal vein as well as poor hepatic reserves are not suitable for TACE. However, it remains controversial about the stopping rule of TACE after multiple cycles of treatment. Several approaches have been attempted to improve the treatment TACE by, namely combination with targeted agents such as sorafenib or axitinib, or by using alternative chemotherapy regimen for intra-arterial injection. On the other hand, there has recently been one study suggesting bland embolization (TAE) may be equally efficacious as the TACE. During the lecture, the key data of important trials and related controversies will be discussed to highlight recent advances in TACE to help the HCC patients.

**How Do We Choose between Microwave Ablation or RFA
for HCC?**

8 July 2016 (Friday), 15:00–15:15

Riccardo Lencioni

Professor of Radiology and Director, Interventional Oncology Research,
Department of Interventional Radiology, University of Miami Miller
School of Medicine, USA

Will be presented at the meeting.

Combination Therapy of TACE and RFA for HCC

8 July 2016 (Friday), 15:15–15:30

*Min-Shan Chen*Chair, Department of Hepatobiliary Surgery, Sun Yat-Sen University
Cancer Center, China

Patients and Methods: A randomized controlled trial was conducted on 189 patients with HCC less than 7 cm at a single tertiary referral center between October 2006 and June 2009. Patients were randomly assigned to receive TACE combined with RFA (TACE-RFA; n 94) or RFA alone (n 95). The primary end point was overall survival. The secondary end point was recurrence-free survival, and the tertiary end point was adverse effects.

Results: At a follow-up of 7 to 62 months, 34 patients in the TACE-RFA group and 48 patients in the RFA group had died. Thirty-three patients and 52 patients had developed recurrence in the TACE-RFA group and RFA group, respectively. The 1-, 3-, and 4-year overall survivals for the TACE-RFA group and the RFA group were 92.6%, 66.6%, and 61.8% and 85.3%, 59%, and 45.0%, respectively. The corresponding recurrence-free survivals were 79.4%, 60.6%, and 54.8% and 66.7%, 44.2%, and 38.9%, respectively. Patients in the TACE-RFA group had better overall survival and recurrence-free survival than patients in the RFA group (hazard ratio, 0.525; 95% CI, 0.335 to 0.822; P 0.002; hazard ratio, 0.575; 95% CI, 0.374 to 0.897; P 0.009, respectively). There were no treatment-related deaths. On logistic regression analyses, treatment allocation, tumor size, and tumor number were significant prognostic factors for overall survival, whereas treatment allocation and tumor number were significant prognostic factors for recurrence-free survival.

Conclusion: TACE-RFA was superior to RFA alone in improving survival for patients with HCC less than 7 cm.

Session 8: State-of-the Art Lecture

Stereotactic Body Radiation Therapy for HCC

8 July 2016 (Friday), 16:10–16:40

Jinsil Seong

Professor, Department of Radiation Oncology, Yonsei University College of Medicine, Korea

Radiotherapy produces substantial local antitumor effect, which makes its application increasing in management of hepatocellular carcinoma (HCC). In particular, stereotactic body radiotherapy (SBRT) has shown high local control rate and tolerable toxicity profiles through many publications both retrospective and prospective setting, making SBRT as one of popular modalities for the management of HCC. SBRT uses ablative dose of radiation within short time span. Therefore, it cannot be applied to HCC in general, but to certain indications; the tumors no more than 5 cm in maximal diameter, a certain volume of the liver preserved, and avoidance of close proximity to sensitive organs such as gastrointestinal tract.

In SBRT, a biologically equivalent dose >100 Gy is delivered using highly conformal, hypofractionated radiation technique. This technique requires sophisticated treatment planning, special devices for patient immobilization, as well as precise image guidance to deliver high dose of radiation to tumors in 1 to 5 fractions. Given the steep dose fall-off and reduced number of fractions, the risk of local failure and normal tissue injury due to geometric miss is high with SBRT. Thus, major challenges are to achieve safe and accurate SBRT for intrahepatic tumors by defining and limiting respiratory liver motion during treatment and providing accurate daily image-guidance. Therefore, high-end radiotherapy machines are recommended for SBRT although it is technically possible in a variety of radiotherapy technique from 3-dimensional conformal radiotherapy (3D-CRTs), intensity modulated radiation therapy (IMRT) to SBRT-dedicated machines are also used such as Cyberknife.

SBRT is effective alone but its usefulness as a bridging therapy prior to liver transplantation has also been reported. In this presentation, clinical outcome of SBRT with its practical point in real practice will further be discussed.

Session 10: Surgical Treatment

Is There a Role in 'Down-Staging' Treatment for HCC?

9 July 2016 (Saturday), 08:30–08:50

Pierce Kah-Hoe Chow

Senior Consultant, National Cancer Centre Singapore, Singapore

Liver cancer (HCC or hepatocellular carcinoma) is the 5th most important cancer in the world and the 2nd most important cause of cancer mortality. Surgical resection (and, in carefully selected patients, liver transplantation and radio-frequency ablation) for early stage HCC offers the opportunity for good overall survival (OS) exceeding 60% at 5 years.

Not all cases that can be surgically resected in the technical sense are however in the early stages of the cancer. Prognosis with surgical resection in locally advanced HCC is significantly poorer and in some cases may be inferior to newer efficacious loco-regional therapy such as radio-embolization with Yttrium-90.

In many common cancers (other than liver) such as breast or colorectal cancers, a standard surgical oncology approach with intermediate stage or locally advanced cancer is neo-adjuvant therapy to downstage the cancer to a more early tumor stage where surgical resection can result in better long-term survival or hopefully even cure. Such down-staging can be achieved with a combination of chemotherapy or radiation therapy.

There have previously been very few reports of successful down-staging for HCC. Most of these have involved combinations of chemotherapy drugs, are relatively toxic and more importantly the outcomes have been frequently difficult to predict.

Recent developments in radiation therapy in HCC have been reported to predictably downstage HCC. The results with SIRT have been particularly consistent with HCC, where it has also been shown to cause regression in HCC that has invaded the vasculature. This offers the possibility of conversion of un-resectable locally advanced HCC (such as those involving major blood vessels) to a technically resectable stage and of down-staging technically resectable intermediate stage HCC to early stage cancer where resection potentially results in better long-term survival. Prospective long-term studies are however required to demonstrate if such neo-adjuvant therapy should become standard of care for locally advanced or intermediate-stage HCC. The safety of surgical resection of HCC is discussed in the context of the P4S study and other reports.

Liver Transplantation for Advanced HCC

9 July 2016 (Saturday), 08:50–09:10

Kyung-Suk Suh

Professor and Chairman, Department of Surgery, Seoul National University, Korea

Recurrence of transplant recipients with far advanced hepatocellular carcinoma (HCC) including macrovascular invasion or huge HCC or numerous HCC is common and macrovascular invasion is considered as a contraindication of liver transplantation. A living donor is uniquely matched to a certain recipient and this special relationship between a donor and recipient can provide a patient with the opportunity to undergo liver transplantation even in suboptimal patients with advanced HCC. However, a high probability of tumor recurrence should evoke ethical issues concerning risk to the living donor. There are no accepted criteria for patients with tumors that lie outside the conventional criteria (e.g. Milan criteria).

To expand the Milan criteria, prognostic factors other than size and number of tumor may be necessary. Between November 1997 and December 2005, 104 cases of liver transplantation for patients with HCC were performed at our center. Twenty-four patients did not meet the Milan criteria preoperatively. Among these 24 patients, 19 had no major vascular invasion at the time of surgery. We analyzed the survival and prognostic factors of these 19 patients. The mean follow-up period was 33 months (range 6–89). Three-year survival rate in 19 patients was 67.4%. Three-year survival rates were significantly higher when preoperative alpha-fetoprotein was less than 400 ng/ml (86.2 vs. 0%, $p < 0.001$) when Edmonson-Steiner's histological grade 1 or 2 (100 vs. 40%, $p = 0.036$) and when microvascular invasion was absent (78.6 vs. 30%, $p = 0.039$). Only AFP was a preoperative factor.

Positron emission tomography using F-18 fluoro-2-deoxy-d-glucose (18F-FDG-PET) imaging is now well established as a noninvasive diagnostic tool for the detection of a variety of malignant tumors. However, in the case of HCC, several investigators have reported controversial conclusions and an inadequate sensitivity for PET (50%–55%). Nevertheless, a high positive rate of FDG accumulation has been reported in patients with high-grade HCC and in those with markedly elevated alpha fetoprotein (AFP) levels. When we analyzed the association between tumor factors and PET (+) (greater PET lesion uptake) in liver, preoperative AFP level and vascular invasion were found to be significantly associated with PET (+) ($p = 0.003$ and $p < 0.001$, respectively). The 2-yr recurrence-free survival rate (2-yr RFSR) of PET (–) patients was significantly higher than that of PET (+) patients (85.1% vs. 46.1%) ($p = 0.0005$). PET imaging could be a good preoperative tool for estimating the post-LT risk of tumor recurrence, because histological grade and vascular invasion cannot be determined preoperatively.

The retrospective data of 178 consecutive HCC patients who underwent LDLT from January 2003 to December 2009 in Seoul National University Hospital were collected. We analyzed 113 patients who were evaluated all 3 tests including 18F-FDG PET positivity, serum AFP level and serum PIVKA II level preoperatively. Multivariate analysis showed that serum AFP level, serum PIVKA II level and 18F-FDG PET positivity were statistically significant variables. HCC of all 3 patients with high risk of 3 biological factors and within Milan criteria were recurred. However, HCC of only 1 patient among the 9 patients beyond Milan

criteria and with low risk of biological factors (AFP <100 ng/ml, PIVKA II <100 mAU/ml, PET negative) were recurred.

We did another study about far advanced HCC. 22 transplant recipients with HCC larger than 10 cm or more than 10 numbers or with macrovascular invasion preoperatively from January 2003 to October 2010 were included. 1 year disease free survival (DFS) and 2 year DFS were 40.9% and 23.9%, respectively. 1 year survival rates (SR) and 2 year SR were 71.6% and 59.7%, respectively. 6 patients were without tumor recurrence and the median survival duration was 25.4 (13–85) months and the median survival duration of 16 patients with tumor recurrence was 12.37 (3–40) months. There were no statistical differences of DFS and SR according to macrovascular invasion (MVi) and 2 year SR were 68.2% (no MVi) and 50.9% (MVi). There were no significant different outcomes according to treatment modality. However, there was significant different 2 yr DFS according to serum alpha-fetoprotein level, 54.5% (AFP <200 ng/ml) and 0.00% (AFP >200 ng/ml) after LDLT ($p = 0.023$).

Conclusion: Tumor biological markers have the possibility to overcome the limitation of the Milan criteria. Preoperative serum AFP level, PIVKA II level and 18F-FDG PET positivity of the tumor predict the tumor recurrence better than Milan criteria in living donor liver transplantation for the patients with HCC. The patients with far advanced HCC have usually poor prognosis. However, the patients even with far advanced HCC can have better outcome after living donor liver transplantation if we select the candidates carefully by better selection criteria such as alpha-fetoprotein.

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Choosing the Best Treatment for HCC Using ALBI Score

9 July 2016 (Saturday), 09:10–09:30

Paul B.S. Lai

Professor of Surgery, Department of Surgery, Prince of Wales Hospital/
The Chinese University of Hong Kong, Hong Kong

Most patients with hepatocellular carcinoma (HCC) have associated chronic liver disease, and the severity of liver dysfunction is traditionally measured by Child-Pugh grading. However, Child-Pugh grading requires the use of subjective variables such as presence of ascites and encephalopathy. From an international collaboration, we identified a new objective measure of liver dysfunction that independently influence the survival in patients with HCC.

The model, called the Albumin-Bilirubin score (ALBI score), performed at least as good as the Child-Pugh grading in patients from different geographic regions. From a Cox regression model based on albumin and log₁₀ bilirubin, patients were classified into ALBI-1 (good liver function with minimal dysfunction), ALBI-2 (less good liver function with moderate dysfunction) and ALBI-3 (poor liver function with severe dysfunction). When we used survival data from HCC patients in different geographic regions to validate the model, distinct prognostic groups were identified.

When we applied the ALBI model (using patients' pre-operative serum albumin and bilirubin levels) to study just the Child's A HCC patients, we found the ALBI-1 patients survived significantly better than those of ALBI-2. Such findings confirmed the impact of liver dysfunction on the survival of HCC patients in general.

When we further studied the survival of HCC patients receiving curative therapy, again from cohorts of HCC patients from different geographic regions, we found ALBI-1 patients survived approximately twice as long as those ALBI-2 patients. However, in the cohort of patients receiving curative ablation therapies, there was a similar difference in survival between ALBI-1 and ALBI-2 patients. This implies that a very significant fraction of mortality in HCC patients after potentially curative therapies, even in Child's A patients, is attributable to liver dysfunction. Therefore, for ALBI-2 patients may, where options exist, be more suitable for liver transplantation or the less invasive curative ablative therapies.

The Role of Portal Vein Thrombectomy in Advanced HCC

9 July 2016 (Saturday), 09:30–09:50

Etsuro Hatano

Professor, Hepato-Biliary-Pancreas Surgery, Department of Surgery,
Hyogo College of Medicine, Japan

Background: The prognosis of hepatocellular carcinoma (HCC) with tumor thrombus in the major portal vein has been extremely poor. We investigated the outcome of hepatic resection in HCC with major portal vein tumor thrombus (PVT).

Methods: We retrospectively evaluated 52 consecutive patients who underwent hepatic resection for HCC with tumor thrombi in the first branch or trunk of the portal vein. Factors related to disease-free survival (DFS) and overall survival (OS) were analyzed.

Results: The median DFS and OS times were 8.9 and 27.6 months for the whole cohort, respectively. Multiple tumors (hazard ratio 2.12; 95% CI 1.11–4.33; $p = 0.023$), positive surgical margins (hazard ratio 2.45; 95% CI 1.19–4.81; $p = 0.016$), and non-adjuvant hepatic arterial infusion chemotherapy.

(HAIC; hazard ratio 2.07; 95% CI 1.11–3.90; $p = 0.023$) were independent risk factors for DFS. Non-adjuvant HAIC (hazard ratio 1.84; 95% CI 1.01–3.37; $p = 0.047$) was an independent risk factor for OS. The median OS times in the adjuvant HAIC and non-adjuvant HAIC groups were 33.2 and 21.5 months, respectively ($p = 0.044$). The 1-, 3-, and 5-year OS rates were 77.8, 48.2, and 25.9% in the adjuvant HAIC group and 68.0, 32.0, and 12.0% in the non-adjuvant HAIC group, respectively.

Conclusions: Macroscopically curative resection seems to be of benefit to HCC patients with PVT, even with tumor thrombi in the first branch or trunk of the portal vein. Adjuvant postoperative HAIC might improve DFS and OS in such patients.

Session 11: Imaging

Accuracy of PET-CT in HCC

9 July 2016 (Saturday), 08:30–08:50

Tony Loke

Head of Radiology, Hong Kong Integrated Oncology Centre, Hong Kong

Single tracer of 18F-FDG PET/CT has proven value in Hepatocellular carcinoma (HCC). 18F-FDG PET/CT is superior in detecting extra hepatic HCC than CT and MRI. 18F-FDG PET/CT is able to predict HCC histopathological grades, prognosis and survival rates. Higher SUVmax has been implicated with poorer prognosis and survival rates.

18F-FDG PET guides management and treatment by guiding biopsy of 18F-FDG avid tumors (avoiding necrotic tumors) and is the best imaging modality to monitor treatment response by interval 18F-FDG PET imaging.

However, the greatest disadvantage for single tracer 18F-FDG PET/CT in HCC is the low sensitivity for detecting primary HCC which is between 50–55%.

Recent studies suggested the use of 11C-acetate in conjunction with 18F-FDG (Dual tracer PET/CT) in HCC has several advantages over single tracer. Dual tracer improves the sensitivity and specificity in primary detection and staging of HCC. It is able to differentiate histopathological grades of HCC more reliably which affects patient's prognosis and survival rates. The combination of 11C-acetate and 18F-FDG improves sensitivity and specificity for detection of extra-hepatic metastasis.

The accuracy of dual tracer PET/CT relies on the fact that 11C-acetate has higher sensitivity than 18F-FDG. The tracers are complimentary in that tumors which are both positive on 11C-acetate and 18F-FDG are taken up by different parts of tumors and combining both tracers increase sensitivity to near 100% (Ho et al JNM 2003).

Although stated by Ho that dual tracer compliments one another by increasing sensitivity for the detection of primary HCC, the sensitivity is limited by intrahepatic tumor size (Park et al. 2008). Only 31.8% HCC was detected by 11C-acetate and 27.2% HCC detected by 18F-FDG in small tumor < 2cm. Sensitivity for 11C-acetate was 95.2% and 92.8% for 18F-FDG for HCC greater than 5cm.

According to Ho et al, dual tracer PET is more specific for differentiating HCC from other malignant and benign lesions HCC is very likely if the lesion is avid for both 11C-acetate and 18F-FDG. Non HCC malignancy such as liver metastases and cholangiocarcinoma or poorly differentiated HCC are 18F-FDG avid but not 11C-acetate avid. Benign pathology is likely if the lesions are not 11C-acetate and 18F-FDG avid (hemangiomas FNH and adenoma).

However, 11C-acetate is unable to distinguish HCC from focal nodular hyperplasia or hepatocellular adenoma according to Magini et al (Clinical Nuclear Medicine in 2009). In 31 patients with 43 lesions (36 with FNH, 5 with hepatocellular adenoma, 1 with hepatoma, and 1 with metastasis), Magini found that 5 HA were positive for 18F-FDG, 3 FNH were positive for 18F-FDG and 2 FNH were positive for 11C-acetate. In the prediction of HCC differentiation, well differentiated HCC tends to be 11C-acetate avid and poorly differentiated HCC tends to be 18F-FDG avid.

The role of dual-tracers PET/CT in extrahepatic metastases is more established and can detect extra-hepatic metastatic tumor with diameter >1cm.

¹⁸F-FDG is more sensitive than ¹¹C-acetate, although the difference is not statistically significant. According to Ho et al and our experience, dual tracer PET-CT was more sensitive than FDG alone, contrary to Park et al. 23% of metastatic lesions were detected by C-acetate only. Negative single-tracer cannot reliably exclude metastatic HCC because the negative predictive value of single tracer PET is less than 50%. In addition, dual-tracers PET have incremental value when compare with single-tracer PET in the evaluation of HCC metastasis.

The major inadequacies of dual tracer PET/CT in HCC is that sensitivity for intra hepatic metastasis detection is limited by size especially when tumours are less than 2cm. Specificity has limitations for HCC detection and differentiation as it cannot differentiate inflammation from malignancy. False positive for ¹¹C-acetate avid lesions include AML, dysplastic nodules, shunts, scars and necrotic tumors.

Yet, Dual tracer PET/CT is still the best modality in detecting extra-hepatic metastasis but false negatives may occur in renal metastases.

Is Trimodality Dual Tracer PET/CT the Answer?

In our analysis of 32 HCC from 24 patients, the combination of CT/MRI with dual tracer is superior to CT/MR or dual tracer alone in the detection of HCC. The sensitivity approaches 100% even for small HCC.

Trimodality MRI is more accurate than 4 phase MDCT in HCC. Trimodality Primovist MRI with diffusion weighted imaging may further improves the accuracy for HCC detection which translate to improved prognosis and survival rates. Combined CT/MRI with dual tracer may improves specificity for intrahepatic and extrahepatic lesions as MRI and/or MDCT will differentiate inflammatory lesions (infected bilomas, abscess) from HCC and diffusion weighted imaging detect renal metastases with high accuracy.

How to Differentiate Dysplastic Nodules from HCC?

9 July 2016 (Saturday), 08:50–09:10

Byung-Ihn Choi

Clinical Professor, Department of Radiology, Chung-Ang University Hospital, Korea

The borderline hepatocellular lesions in a cirrhotic liver include dysplastic foci, dysplastic nodules, and early HCC. Dysplastic foci are microscopic lesions with precancerous features, such as small cell change, and therefore are not detectable with in vivo imaging. Dysplastic nodules are precancerous hepatocellular lesions that have dysplastic features without histologic evidence of malignancy. They are subclassified into low-grade dysplastic nodules and high-grade dysplastic nodules on the basis of the degree of cellular abnormalities. Dysplastic nodules are usually 1–1.5 cm in diameter and of a color or size different from that of the background parenchyma. Clinically, high-grade dysplastic nodules are considered precursors of HCC.

Imaging diagnosis plays a crucial role in the evaluation of hepatocarcinogenesis and the early diagnosis of HCC. It is still challenging, however, to accurately characterize borderline hepatocellular nodules, including low-grade dysplastic nodules, high-grade dysplastic nodules, and early HCC, at imaging, because they usually have similar imaging features. Previous studies have shown that conventional US, CT and MRI have limited sensitivity for the detection of early HCC and high-grade dysplastic nodules but that MRI with hepatobiliary contrast media has promise for this purpose.

Ultrasound is used as a surveillance examination for HCC in cases of chronic liver disease and cirrhosis, although this examination has limited sensitivity and specificity in early stage HCC, including borderline hepatocellular nodules. Nodules larger than 1 cm found at ultrasound surveillance of a cirrhotic liver should be investigated further with a diagnostic test. Contrast-enhanced CT and dynamic MRI are the primary diagnostic tests for the diagnosis of HCC; if the nodule has the typical hallmark of hypervascularity in the hepatic arterial phase with washout in the portal venous or delayed phase, a definitive diagnosis of HCC can be made. If the findings are not characteristic or the vascular profile is not typical, a second contrast-enhanced imaging study, such as dynamic MRI with a hepatobiliary contrast agent can be performed. When a hypovascular nodule larger than 1 cm has one or more suggestive signs of HCC during a secondary test, including hypointensity in the hepatobiliary phase of gadoxetic acid enhancement, defect in the Kupffer cell phase of perflubutane-enhanced US or hyperintensity at DWI, biopsy is preferred to imaging follow-up. If a hypovascular nodule does not exhibit any suggestive sign of malignancy, imaging follow-up is recommended.

Intraoperative Imaging for HCC

9 July 2016 (Saturday), 09:10–09:30

Norihiko Kokudo

Professor, Graduate School of Medicine, The University of Tokyo, Japan

During liver resections for hepatocellular carcinoma (HCC), intra operative imaging is indispensable for accurate staging and operative guide for precise liver resection. Intra-operative ultrasound (IOUS) has been a mainstay in intra operative imaging and is regarded one of the most sensitive modality to detect small liver lesions. Since 2007, a second generation contrast medium, Sonazoid, has been widely applied in Japanese centers. Contrast enhanced-IOUS using Sonazoid provides unique Kupffer phase images and they have been reported even more sensitive. Real-time tissue elastography (RTE) is another innovative tool that informs the surgeon about tissue elasticity by applying the principle of ultrasonography. RTE visualizes information regarding tissue elasticity by estimating the strain modules from radiofrequency signals during external compression. Intra-operative RTE can differentiate malignant from benign liver tumors by analyzing elasticity patterns. Recent advance in ICG fluorescence imaging enabled us to visualize HCC lesions because most of the well- to moderately differentiated HCC cells can uptake ICG into cancer cells. ICG is also accumulated in liver parenchyma surrounding poorly differentiated HCCs. In these cases a ring shaped fluorescence can be visualized. ICG fluorescence imaging is also useful for identification of liver segments during anatomic liver resection.

Real-time virtual sonography (RVS) is an innovative imaging technique that can display reconstructed images of computed tomography (CT) and/or magnetic resonance (MR) according to acurrently scanned ultrasound image. We have been developing a new navigation system for liver resection using both 3-D simulation and RVS.

The Key for Accurate Assessment of HCC after TACE

9 July 2016 (Saturday), 09:30–09:50

Jean-Francois H. Geschwind

Chairman of Radiology and Biomedical Imaging, Professor of Radiology
and Oncology, Yale University School of Medicine, USA

Will be presented at the meeting.

Session 12: Minimal Invasive Surgery

Training of Laparoscopic Liver Resection for Future Generation Surgeons

9 July 2016 (Saturday), 10:35–10:55

Go Wakabayashi

Director, Department of Surgery, Ageo Central General Hospital, Japan

The laparoscopic procedure is more difficult to master than the open procedure because of the movement restrictions imposed upon us when we operate from outside the body cavity. However, good visibility of the operative field especially around the liver, which is located beneath the costal arch, and the magnifying provide for neat transection of the hepatic parenchyma. Another theoretical advantage is that pneumoperitoneum pressure reduces hemorrhage from the vein with low pressure. Therefore, laparoscopic liver resection (LLR) is superior to open liver resection (OLR) because the laparoscope allows better exposure with a magnified view, and the pneumoperitoneal pressure reduces hepatic vein bleeding from the cut surface. The concept for liver resection has changed from the open ventral approach to the laparoscopic caudal approach. The important structures such as the hilar plate and the vena cava are clearly viewed just in front of you by the laparoscopic caudal approach. The better exposure with pneumoperitoneum is the main driving force that I began pure laparoscopic living donor hepatectomy based on our experience of laparoscopy-assisted donor hepatectomy. The most dangerous event that can happen during liver surgery is the injury of major vessels. As long as you see it clearly, you will never injure it without knowing it. All these aspects should be well propagated to our future generation surgeons. At the 2nd International Consensus Conference on Laparoscopic Liver Resection in Morioka, both experts and jury recognized the need for a formal structure of education for those interested in performing major LLR because of the steep learning curve.

How to Perform Laparoscopic Anatomical Liver Resection?

9 July 2016 (Saturday), 10:55–11:15

Ho-Seong Han

Professor, Department of Surgery, Seoul National University Bundang Hospital, Korea

With many reports on encouraging outcomes, laparoscopic liver resection has been accepted as attractive alternative for open liver resection. Hepatocellular carcinoma (HCC) is associated with chronic liver disease and cirrhosis. When a patient undergoes liver resection, surgeons must consider the volume and function of the remnant liver because patients with liver cirrhosis are predisposed to hepatic failure after major resection. Therefore, it is better to preserve the liver volume as far as possible, even during laparoscopic surgery. Resection must be performed with a full understanding of anatomical liver resection. Because HCC spreads to the remnant liver through portal tributaries, anatomical resection of the surrounding portal vein has a theoretical advantage over nonanatomical resection in terms of oncological clearance. Anatomical liver resection can be performed in many ways. Ultrasound-guided selective portal venous occlusion has been examined for use in anatomical resection. Makuuchi performed complete or partial anatomical resections of liver segment tumors based on portal anatomy, guided by intraoperative ultrasonography. Glissonian pedicle approach is one method for anatomical liver resection. The Glissonian approach can also be used in any type of laparoscopic anatomical liver resection.

The objective of the present study was to share the important technical features of LLR using the Glissonian pedicle method, which should provide important information to guide resection and reduce blood loss from the liver parenchyma during LLR. The type of resection also may depend on the remaining liver's functional capacity. Therefore it would be recommendable to resect as minimal as possible without jeopardizing oncologic safety. In conclusion, anatomical liver resection may be advantageous in terms of preserving remaining liver volume and eradicating tumor completely.

An Update on Robotic Surgery for Liver Cancer

9 July 2016 (Saturday), 11:15–11:35

Jia-Hong Dong

Professor and Executive President, Department of Hepatobiliary Surgery,
Tsinghua University, Beijing Tsinghua Changgung Hospital, China

Robotic liver resection is safe and feasible for experienced surgeons with advanced laparoscopic skills [1, 2]. Despite of longer operative times, robot-assisted surgery could extend indication of minimally invasive hepatectomy [3–6], as well as increase percentage of major hepatectomies to be performed in a purely minimally invasive fashion [7]. Although the range of instruments available for robotic liver surgery is currently much smaller than for laparoscopic or open techniques [8], some precise manipulation could be realized more conveniently under the assistance of robot [9]. Therefore, we suggest choose robotic approach for lesions located in the technically challenging anatomic area, or in contact with main liver vessels, or requiring precise manipulation including porta dissection, laparoscopic suture, vascular anastomosis and lymphadenectomy. Long-term oncologic outcomes of robotic approach are unclear, but the short-term perioperative outcomes are comparable to those utilizing the laparoscopic and open approaches [1, 10]. Further studies are needed in terms of oncologic and cost-effectiveness outcomes [11].

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**Safe Laparoscopic Liver Resection in Cirrhotic Liver –
Hong Kong Experience**

9 July 2016 (Saturday), 11:35–11:55

*Tan-To Cheung*Associate Professor, Department of Surgery, The University of Hong
Kong, Queen Mary Hospital, Hong Kong

Liver resection for patients with cirrhosis remains a challenging operations. The presence of thrombocytopenia and portal hypertension could lead to severe bleeding during hepatectomy. The enthusiasm of laparoscopic hepatectomy has been growing and many studies have reported their initial favorable results for patients with HCC. The advancement in technology, better understanding of the use of pneumoperitoneum pressure and more experience accumulated make laparoscopic liver resection for patients with cirrhosis possible.

In Queen Mary Hospital, we have performed more than 350 liver resection under laparoscopic approach. These included a high percentages of patients with HCC and underlying liver cirrhosis.

Favorable outcome may be achieved if the patients are carefully selected and carried out in high volume centers.

Session 13: Hepatatrophy

Implication of Long-Term Hepatitis B Treatment for HCC Development

9 July 2016 (Saturday), 10:35–11:00

Man-Fung Yuen

Chair Professor, Department of Medicine, The University of Hong Kong, Hong Kong

Will be presented at the meeting.

Prevention of HBV Related HCC in Asia

9 July 2016 (Saturday), 11:00–11:25

Ji-Dong Jia

Professor of Medicine, Beijing Friendship Hospital, Capital Medical University, China

The most common risk factor for hepatocellular carcinoma (HCC) is chronic HBV infection, which accounts for more than 50% of all cases globally and 60% to 80% in some Asian countries. Strategies to prevent HBV-related HCC include primary, secondary prevention, and tertiary preventions.

Primary Prophylaxis of HBV-Related HCC: Vaccination to Decrease the Rate of HBV Infection

The universal vaccination programs carried out in countries with endemic HBV have resulted in a significant decline in the prevalence rate of HBsAg and incidence of HCC. A national survey showed that the prevalence of HBsAg declined from 9.75% in 1992 to 7.18% in 2006 in China mainland where universal infant HBV vaccination started in 1992. Furthermore, a recent report of a 30-year follow-up study demonstrates that HCC incidence rate also decreased by 84% in vaccinated cohort in Qidong area of eastern China.

Secondary Prophylaxis of HBV-Related HCC: Antiviral Treatment to Reduce Incidence of HCC in Chronic HBV Infection

A large-scale cohort study (REVEAL study) carried out in Taiwan demonstrated that the incidence rates of HCC was correlated with serum viral load during a mean follow-up of 11.4 years. Even patients with moderate HBV-DNA level (60–2000 IU/ml) also had a substantially increased risk of HCC and mortality compared with uninfected individuals.

RCT studies and meta-analyses confirmed the beneficial effect of antiviral treatment on reducing HCC risk, no matter using lamivudine, adefovir, entecavir, tenofovir or interferon. A follow-up study showed that entecavir is more effective than lamivudine in prevention of HCC due to higher potency and minimal risk of resistance.

Of note is that suppression of viral replication in CHB patients by antiviral treatment could reduce but do not eliminate the risk of HCC, especially in patients with cirrhosis. Therefore, regular surveillance is important in patients receiving antiviral therapy even in patients who loss HBsAg in order to detect tumors at an early stage.

Tertiary Prophylaxis of HBV-Related HCC: Adjuvant Antiviral Treatment to Prevent Recurrence in HCC Patients After Curative Therapies

In patients of HCC, high HBV-DNA level was significantly associated with recurrence after tumor resection (OR = 2.548). Studies show that antiviral treatment with nucleos(t)ide analogs could decrease HCC recurrence and improve postoperative survival. Meta-analysis also demonstrated that adjuvant antiviral therapy with nucleos(t)ide analogues could reduce the recurrence after curative therapy or TACE.

Risk Stratification of HBV-Related HCC

9 July 2016 (Saturday), 11:25–11:50

Kwang-Hyub Han

Professor, Department of Internal Medicine, Yonsei University College of Medicine, Korea

HCC develops in the context of readily identifiable risk factors. Therefore, it is important to stratify high-low risk populations by risk prediction using clinical profiling to guide monitoring and surveillance for high-risk patients. The risk of HCC in patients with chronic HBV infection is not same and increases in parallel to aging, male gender, necro-inflammatory disease activity, and degree of advanced liver disease.

To date, HCC risk prediction models had been suggested through incorporating well-known risk factors for patients with chronic hepatitis B (CHB). To stratify risk for HBV-related HCC development, the risk factors such as male sex, old age, advanced liver fibrosis or cirrhosis, and a high HBV-DNA level, have been extensively studied. Several HCC risk scoring systems to predict HCC development were derived and validated in patients with CHB cohorts, when antiviral therapy was not widely available. Before the era of effective antiviral therapy, patients with chronic HBV infection were at high risk according to active viral replication. For example, in REACH-B HCC risk score, HBV-DNA levels can accurately determine the risk of HCC development.

As HBV related chronic liver disease is a progressive disease and patients with cirrhosis are at high risk, effective control virus by potent antiviral therapy can reduce the prognostic roles of viral factors by not eliminating but reducing the risk of HCC. The HCC scoring systems based on the fibrotic burden rather than serum HBV-DNA levels using the non-invasive fibrosis marker would be helpful in delicate risk stratification. Therefore, risk scores should be reevaluated. The GAG-HCC and CU-HCC scores were derived from hospital cohorts including cirrhosis as a major risk factor. However, the diagnosis of cirrhosis based on routine imaging and clinical parameters can be inaccurate. Recent studies have demonstrated that the liver stiffness (LS) value using transient elastography (TE) is useful for predicting upcoming HCC occurrence. These results suggest that the individual's risks should be assessed based on the fibrotic burden rather than a biological gradient of serum HBV-DNA levels in this era of antiviral therapy. In recent Korean study, the modified REACH-B model, which serum HBV-DNA level of the original REACH-B score was substituted with the LS value using TE, had the better predictive performance compared with the conventional risk prediction models among patients with successful antiviral therapy.

Session 14: Debate Session

HKLC Is a Better Staging System Than BCLC for HCC Management (Pros)

9 July 2016 (Saturday), 14:00–14:40

Ronnie Poon

Honorary Clinical Professor, Department of Surgery, The University of Hong Kong, Hong Kong

Management of HCC is a challenging task because tumors often present late, and the majority of patients have impaired liver function reserve due to underlying viral chronic hepatitis or cirrhosis. It is also complicated by the availability of many different treatment options. How to choose the best treatment for a HCC patient based on tumor stage and liver function to provide the best long-term survival result is the critical issue faced by clinicians managing HCC.

Prior to the Hong Kong Liver Cancer (HKLC) staging system, the Barcelona Clinic of Liver Cancer (BCLC) staging was the most popular staging for liver cancer used worldwide because it was the only staging system with treatment guidelines. The BCLC staging was developed based on experience of treatment of liver cancer in the West, and the guidelines are considered too conservative by many Asian liver cancer experts. In particular, patients with multifocal tumors or macroscopic venous invasion in the liver are considered contraindications for surgery. They are recommended for palliative treatment with transarterial chemoembolization or molecular targeted therapy instead in BCLC staging.

HKLC staging is a new liver cancer staging system with treatment guidelines derived from statistical analysis of more than 3800 consecutive HCC patients treated by different modalities. The HKLC system refined HCC staging into 5 stages using simple tumor parameters (size, number, vascular invasion, metastasis) together with Child class and ECOG performance status, and recommended more aggressive surgical treatment to patients with multifocal tumors or macroscopic venous invasion confined to the liver. Statistical analysis showed that treatment according to HKLC staging doubled overall median survival of patients compared to BCLC staging (16.6 vs. 8.9 months). Notably, even patients with multiple tumors or vascular invasion had a 5-year survival rate of 50% compared with 0% if treated with drug therapy alone as recommended by BCLC staging, and a portion of these patients were cured by surgery.

HKLC Is a Better Staging System Than BCLC for HCC Management (Cons)

9 July 2016 (Saturday), 14:00–14:40

Riccardo Lencioni

Professor of Radiology and Director, Interventional Oncology Research,
Department of Interventional Radiology, University of Miami Miller
School of Medicine, USA

Will be presented at the meeting.

HCC with Intrahepatic Portal Vein Tumour Thrombus Should Be Treated by Systemic Rather Than Transarterial Therapy (Pros)

9 July 2016 (Saturday), 14:40–15:20

Yi-Hsiang Huang

Professor, Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taiwan

Hepatocellular carcinoma (HCC) is the sixth most common malignant disease and third most frequent cause of cancer death worldwide. HCC is prevalent in East Asia and sub-Saharan Africa, an endemic area of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. In early stage of HCC, either surgical resection, percutaneous ablation, or liver transplantation is a potential curative option and may provide 5-year survival rate up to 75 %. For patients not suitable for curative treatment, transarterial chemoembolization (TACE) can provide locoregional tumor control to increase survival. Portal vein tumor thrombosis (PVTT) of HCC is usually associated with a poor prognosis and is found in approximately 10–40 % of patients at diagnosis. Sorafenib, a multikinase inhibitor is currently the standard of care for HCC patients with PVTT according to AASLD and EASL guidelines. In the sub-group analyses of the Asia-Pacific trial, patients with MVI and/or extrahepatic metastasis, sorafenib showed a better clinical outcome than placebo arm with a median overall survival of 5.6 months. Due to improvement in treatment modalities and patient selection, transarterial therapy is no longer absolute contraindicated for HCC with PVTT, but the risk of treatment-induced ischemia and liver failure should be recognized. One study applied TACE in HCC patients (n=84) with PVTT, the OS was 7.1 months. The extent of PVTT is a factor associated with the outcome. Even though, TACE plus sorafenib combination treatment with TACE did not show additional survival benefit as compared with sorafenib monotherapy for PVTT HCC cases. Transarterial radioembolization (TARE) is an option for HCC patients with PVTT. Down-staging to enable liver resection or transplantation could possibly be achieved with TARE in certain cases. The median OS ranged from 5.6 to 10.4 months depending on the extent of PVTT. However, there is no solid data from randomized controlled trials to support that TARE is superior to systemic targeted therapy in HCC patients with PVTT. Based on current evidences from published studies and guidelines, HCC patients with PVTT should be treated by systemic targeted therapy as the first line treatment at present.

HCC with Intrahepatic Portal Vein Tumour Thrombus Should Be Treated by Systemic Rather Than Transarterial Therapy (Cons)

9 July 2016 (Saturday), 14:40–15:20

Jean-Francois H. Geschwind

Chairman of Radiology and Biomedical Imaging, Professor of Radiology and Oncology, Yale University School of Medicine, USA

Will be presented at the meeting.

Session 15: Debate Session

Liver Resection Is Better Than Ablation for Early HCC (<3 cm) (Pros)

9 July 2016 (Saturday), 14:00–14:40

Ho-Seong Han

Professor, Department of Surgery, Seoul National University Bundang Hospital, Korea

Ablative treatments have been used widely as an alternative of liver resection. Some reports showed similar outcomes when compared to liver resection. However the ablative procedure has limitation in applying for tumor located close to vessels, or adjacent organs. And there are reports on treatment failure in several cases.

Most of the comparative studies are between ablation and open liver resection.

Recently laparoscopic liver resection is becoming standard procedure in tumorectomy.

This procedure has several advantages of minimal morbidity without compromising oncologic safety.

If the operation can be performed with minimal invasive surgery, the advantages of the liver resection are rather more increased. Especially, the tumor less than 3 cm in size, the morbidity of laparoscopic live resection is very little.

In conclusion, liver resection may be advantageous in terms of minimal morbidity and eradicating tumor completely.

**Liver Resection Is Better Than Ablation for Early HCC
(<3 cm) (Cons)**

9 July 2016 (Saturday), 14:00–14:40

Jia-Hong Dong

Professor and Executive President, Department of Hepatobiliary Surgery,
Tsinghua University, Beijing Tsinghua Changgung Hospital, China

Will be presented at the meeting.

ALPPS Is More Effective Than PVE for HCC in Patients with Inadequate Future Liver Remnant (Pros)

9 July 2016 (Saturday), 14:40–15:20

Albert Chan

Associate Professor, Division of Hepatobiliary and Pancreatic Surgery, and Liver Transplantation Department of Surgery, The University of Hong Kong, Hong Kong

Background: ALPPS has been introduced as a novel approach to induce liver hypertrophy in patients with insufficient future liver remnant (FLR) contemplating for major hepatectomy in colorectal liver metastasis. Our aim was to evaluate the suitability and outcome of ALPPS for hepatitis-related HCC when compared with portal vein embolization (PVE).

Methods: Patients with Child A cirrhosis and FLR <35% of estimated total liver volume (ESLV) were selected for ALPPS. In-situ split was performed by anterior approach in stage I. Portal haemodynamics were studied intraoperatively. No bag nor drain was placed in stage I. Postoperative outcomes were compared with PVE matched for age, liver function and tumor characteristics.

Results: From October 2013 to May 2016, 29 patients with a median age of 60 (hepatitis B, n = 28; hepatitis C, n = 1) underwent ALPPS. The tumor size was 8.6 cm (1.3–17.0 cm). Preoperative FLR was 313.0 ml and the median FLR/ESLV was 26.1% with an ICG value at 15 minutes of 11.3%. Portal flow to FLR increased from 200.0 ml/min to 542.5 ml/min after portal vein ligation, and subsequently to 737.5 ml/min after in-situ split. As a result, FLR volume increased by 50.7% after 6 days with an FLR of 498.3 ml and FLR/ESLV of 38.5%. All patients proceeded to stage II operations (right trisectionectomy, n = 4; extended right hepatectomy, n = 10, right hepatectomy n = 15) without inter-stage complications. ALPPS induced greater FLR hypertrophy than PVE (daily FLR gain: 7.0% vs. 0.8%, p < 0.001) without increased morbidity (10.3% vs. 32.1%) and mortality (6.9% vs. 7.1%, p = 1.000). The 1-year tumor recurrence rate for ALPPS and PVE were similar (TNM I/II: 0% vs. 20.5%; TNM III: 53.8% vs. 52.2%, respectively).

Conclusion: ALPPS induced FLR hypertrophy in chronic liver disease by substantial flow augmentation. The entire course of treatment could be completed in a timely manner within one hospitalization.

Table 1.

(Median)	ALPPS (n = 22)	PVE (n = 56)	P-value
Age	62	62	0.722
Tumor size, cm	6.8	6.8	0.714
Serum aspartate aminotransferase, u/l	51.5	45.0	0.617
Albumin, g/l	39.5	40	0.624
Liver status			
Cirrhosis	12	40	0.101
Chronic hepatitis	11	16	
ESLV, ml	1,241.5	1,247.4	0.824
Pre-ALPPS/PVE			
FLR, ml	297.0	302.0	0.613
FLR:ESLV %	24.6	24.7	0.477
Post-ALPPS/PVE			
FLR, ml	503.8	427.8	0.089
FLR:ESLV%	39.6	34.8	0.061
Gain in volume per day	7.0%	0.8%	<0.001
Time to hepatectomy, days	6	48	<0.001
Overall complication rate	7 (30.4%)	18 (32.1%)	0.978
Clavien complication 3a or above	7 (30.4%)	15 (26.8%)	0.657
Hospital mortality	1 (4.3%)	4 (7.1%)	1.000

ALPPS Is More Effective Than PVE for HCC in Patients with Inadequate Future Liver Remnant (Cons)

9 July 2016 (Saturday), 14:40–15:20

Norihiro Kokudo

Professor, Graduate School of Medicine, The University of Tokyo, Japan

Two-stage hepatectomy combined with in-situ splitting of the liver and concomitant portal ligation during the 1st stage has been sporadically performed since at least 2007 in Germany and rapid hypertrophy of the future liver remnant (FLR) has been associated with this procedure more than that with the conventional portal vein embolization (PVE). Since the first preliminary report in 2011, this innovative idea rapidly expanded in European and South American countries, called as Associating Liver Partition and Portal vein embolization for Staged hepatectomy (ALPPS). ALPPS has been associated with a 60%–80% increase of the original FLR volume during 7–10 days, and with more than 95% of feasibility of two-stage hepatectomy. However, ALPPS has been associated with 80% of morbidity and 9%–12% of the mortality rate. Since hepatocellular carcinoma (HCC) is frequently accompanied by damaged liver including liver fibrosis or cirrhosis, safety of ALPPS in this setting is more questionable. According to ALPPS registry data, mortality of ALPPS for HCC is slightly higher than that for colorectal liver metastases.

Another concern is retarded liver hypertrophy after ALPPS for damaged liver. Although the rapid growth of FLR after the ALPPS procedure is very impressive in normal liver, such data for damaged liver are still limited.

Finally, indication of ALPPS in HCCs may be very small because most of the cases can be resected by hemihepatectomy with or without PVE. Right trisectionectomy with insufficient FLR is rarely attempted for HCC.

Session 16: BMS Sponsored Symposium

Immunotherapy for HCC – Are We Ready for the Prime Time?

9 July 2016 (Saturday), 15:50–16:40

Thomas Yau

Clinical Assistant Professor, Department of Medicine, The University of Hong Kong, Hong Kong

T-cells play a critical role in immune responses against cancer. Cytotoxic T-lymphocytes (CTL) are one class of effector T-cells that secrete cytokines and can specifically lyse target cells. However, on prolonged antigenic stimulation, T-cells may lose their effector functions even in the presence of antigens that they target. Such an ‘exhaustion’ state renders T-cells incapable of clearing pathogens or eliminating neoplastic cells. Immune checkpoints provide a regulatory feedback mechanism to limit the effector phase of T cell differentiation. They play key parts in tolerance to self antigens, and provide the basis for fine-tuning of the T-cell response. PD1 is a transmembrane receptor. It binds to two ligands, programmed cell death protein 1 ligand 1 (PDL1), and PDL2, both of which are transmembrane proteins as well. PDL1 expression is a major mechanism by which tumor cells can evade immune attack.

Immune checkpoint modulators have recently emerged and offer encouraging results in cancer treatment. Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody and it has been tested clinically in a series of CheckMate studies.

Interaction of hepatocellular carcinoma (HCC) with the immune system plays a major role in its progression. Inadequate co-stimulation, failure of antigen recognition and processing, along with suppression of effector cells are proposed mechanisms that result in weakened immune response in HCC patients. Notably, PD-L1 is over-activated in HCC, and its receptor is found to inhibit T-cell activation. In the presentation, we will discuss about the emerging data about the use of anti-PD 1 in HCC.

Session 17: State-of-the Art Lecture

Systemic Therapy for HCC – The Future and Beyond

10 July 2016 (Sunday), 09:00–09:30

Ann-Lii Cheng

Professor, Department of Internal Medicine, National Taiwan University Hospital, Taiwan

In the past one decade, systemic therapy for HCC has evolved from targeting cancer cells directly by chemotherapy into targeting cancer microenvironment indirectly by anti-angiogenic and immune regulating agents. Multi-targeted anti-angiogenic agents, including sorafenib and regorafenib, have their effect, at least in part, via regulating the tumor vasculature. The recent discovery of immune checkpoint inhibitors further emphasizes the importance of targeting immune microenvironment of HCC.

It has been clear that all immune microenvironments of the cancers are not the same, and individual cancers may benefit from different modes of immune regulation. Liver is an organ that faces abundant toxins and degraded microorganisms derived from the intestine, and has thus evolved into a general immune tolerance state. Further, HCC often emerges from a chronically inflamed liver, accompanied with cirrhosis. Although how these facts may shape HCC immune microenvironment remains far from clear, several known features of HCC may be valuable in future drug development. For examples, Kupffer cells of HBV-related HCC express high level of galectin-9, the ligand of Tim-3; and Tim-3 is an immune checkpoint molecule frequently expressed on the effector T cells of HCC, suggesting a role anti-Tim-3 in the treatment of HCC. Further, M2-polarized macrophages and myeloid-derived suppressor cells (MDSC) are abundant in HCC, suggesting a role of CSF-1R inhibitors or IDO inhibitors. There are many newly discovered features of HCC immune microenvironments, such as specific B cell subtypes (marginal infiltrating CXCR-3 (+) B cells or PD-1^{high} regulatory B cells) which facilitate HCC progression, or Wnt/ β -catenin activation which is a common genetic alteration of HCC that may cause T cell depletion. Further exploration of these HCC-specific immune microenvironment will lead to next generation of HCC-specific immunotherapy.

Session 20: Evidence-Based Systemic Therapy

An Odyssey from Doxorubicin to Nivolumab with Sorafenib and Regorafenib in between

10 July 2016 (Sunday), 09:30–09:55

Ghassan Abou-Alfa

Physician, Memorial Sloan Kettering Cancer Center, USA

Doxorubicin has remained the mainstay and a subject of debate for the treatment of primary liver cancer for almost 40 years. After the first report on the use of doxorubicin for the treatment of advanced and metastatic HCC emerged in the seventies, an endless number of studies have contested its validity as a single agent therapy. In the interim sorafenib a multikinase inhibitor emerged as the standard of care for patients with advanced HCC based on two phase III randomized clinical trials against placebo, conducted in the western hemisphere and the Asia Pacific region. Two efforts since tried to leverage any possible role for doxorubicin via combining it: The first with other chemotherapeutic agents: 5-fluorouracil, cisplatin, and interferon (PIAF), and the latest to be reported in combination with sorafenib. The latter is especially of critical importance considering the supportive randomized phase II data and pre-clinical models that explain a synergistic effect between sorafenib and doxorubicin. Both unfortunately did not show any improvement in outcome the first against doxorubicin and the second against sorafenib. Sorafenib, a multityrosine kinase inhibitor that lacks a specific target was also tested against multiple more robust anti-angiogenic agents in multiple phase III clinical trials, and repeatedly came out as the winning choice. In the midst of this, immune checkpoints were recognized as a potential target for the treatment of HCC in view of high PD-1 and PD-L1 expression in HCC add to a relatively high mutational load and encouraging phase II data showing never witnessed radiologic response rates in the range of 15 to 20%. While in the midst of these novel immune checkpoint inhibitors, new data came in regard to another multikinase regorafenib that barely differ from sorafenib with shockingly positive results in the second line setting versus placebo and after sorafenib failure!

An Update on Transarterial Chemoembolization Trial

10 July 2016 (Sunday), 09:55-10:20

Riccardo Lencioni

Professor of Radiology and Director, Interventional Oncology Research,
Department of Interventional Radiology, University of Miami Miller
School of Medicine, USA

Will be presented at the meeting.

Harnessing the Immune System against HCC

10 July 2016 (Sunday), 10:20–10:45

Han-Chong Toh

Deputy Director, Division of Medical Oncology, National Cancer Centre
Singapore, Singapore

Will be presented at the meeting.

Oral Sessions

Session 9: Best Oral Presentation

0021

The Hepatitis Viral Status in 3843 Hepatocellular Carcinoma Patients from Taiwan Liver Cancer Network

Shiu-Feng Huang¹, Il-Chi Chang^{1,2}, Pei-Jer Chen³, Chi-Ling Chen³, Tseng-Chang Yen⁴, Yun-Fan Liaw²

¹Institute of Molecular and Genomic Medicine, National Health Research Institutes, Miaoli, ²Liver Research Unit, Chang Gung Memorial Hospital Linko Branch, Chang-Gung University, Taoyuan, ³Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, ⁴Department of Applied Mathematics and Institute of Statistics, National Chung-Hsing University, Taichung, Taiwan

Objective: Hepatocellular carcinoma (HCC) is the leading cancer death in Taiwan. Chronic viral hepatitis infections have long been considered as the most important risk factors for HCC in Taiwan. The previously published reports were either carried out by individual investigators with small patient numbers or by large endemic studies with limited viral marker data.

Method: Through collaboration with five medical centers across Taiwan, Taiwan liver cancer network (TLCN) was established in 2005. All participating centers followed a standard protocol to collect liver cancer patients with their biosamples and clinical data. In addition, detailed viral marker analysis, which included HBsAg, HBV DNA, HBV genotype, anti-HCV, HCV RNA and HCV genotypes were also performed.

Results: This study include 3843 HCC patients with available blood samples in TLCN (recruited from November 2005 to April 2011). There were 2,153 (56.02%) patients associated with HBV (HBV group); 969 (25.21%) with HCV (HCV group); 310 (8.07%) with both HBV and HCV (HBV+HCV group); and 411 (10.69%) were negative for both HBV and HCV (non-B non-C group). Two hundred and two of the 2463 HBV patients (8.20%) were HBsAg(-), but HBV DNA (+). The age, gender, cirrhosis, viral titers and viral genotypes were all significantly different between the above 4 groups of patients.

Conclusions: This is the largest detailed viral hepatitis marker study for HCC patients in the literatures. Our study provided novel data on the interaction of HBV and HCV in the

HCC patients and also confirmed that the HCC database of TLCN is highly representative for Taiwan and has become the most important resource for HCC research.

0047

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

Bo Hyun Kim, Joong-Won Park, Jin Sook Kim, Sook-Kyung Lee, Eun Kyung Hong

National Cancer Center, Goyang, Republic of Korea

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

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

Results: Of 47 patients, 3 had combined HCC and cholangiocarcinoma. The predominant etiology for HCC was hepatitis B virus (72.3%). Most patients had preserved liver function (Child-Pugh class A, 89.4%), and 14.9% and 74.5% had vascular invasion or extrahepatic spread, respectively. No intrahepatic tumors were present in 34.0% of the patients. Patients with low CD133 expression tended to have longer progression-free survival (PFS) compared to those with high CD133 expression (5.5 months vs. 4.0 months, respectively; $P = 0.087$), but this was not statistically significant. The expression of other markers was not associated with PFS. When combining two markers, patients with both low CD133 expression and low EpCAM expression demonstrated better PFS compared to those who did not (7.0 months vs. 4.2 months, respectively; $P = 0.037$).

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

0109

Comparison of Patterns and Outcomes of Liver Resection for Hepatocellular Carcinoma between Two Large Centers in the East and the West: A Propensity-Matched Analysis*Tian Yang*^{1,2}, *Parissa Tabrizian*², *Sander Florman*²,
*Wan-Yee Lau*¹, *Jun-Hua Lu*¹, *Meng-Chao Wu*¹,
*Feng Shen*¹, *Myron Schwartz*²

¹Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China; ²Liver Cancer Program, Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, New York, USA

Purpose: Differences of patient characteristics, candidate selection, and surgical practice of liver resection for hepatocellular carcinoma (HCC) have been widely acknowledged between Eastern and Western centers. However, comparative studies between them have been lacking, especially for their surgical safety and long-term efficacy. This study aimed to compare patterns and outcomes of liver resection for HCC between two large hepatic surgical centers in the East and the West.

Patients and Methods: Data were retrospectively collected from those patients who underwent curative resection for HCC in the Eastern Hepatobiliary Surgery Hospital of Shanghai, China (the East group, n = 1,229) and the Mount Sinai Hospital of New York, the United States (the West group, n = 268) from 2000 to 2011. Patients' baseline characteristics, operative variables, perioperative and long-term overall survival (OS) and time-to-recurrence (TTR) were evaluated and compared between the two groups. Propensity score matching analysis was used to minimize bias related to patient selection and confounding variables.

Results: In the entire cohort, the East group had significantly worse liver function and more advanced tumors, but their perioperative mortality and overall and major morbidity rates were comparable between the two groups. By balancing those confounding variables, propensity score matching analysis created 239 pairs of patients in both groups. In the propensity matched cohort, the OS and TTR rates were comparable between the East and West groups (P = 0.396 and P = 0.979).

Conclusions: The present study revealed that a vast heterogeneity of patterns of liver resection for HCC existed between these two large centers from the East and the West, but their surgical safety and long-term efficacy were actually comparable.

0110

Safety and Antitumor Activity of Nivolumab (Nivo) in Patients (pts) with Advanced Hepatocellular Carcinoma (HCC): Interim Analysis of Dose-Expansion Cohorts from the Phase 1/2 CheckMate-040 Study*Bruno Sangro*¹, *Ignacio Melero*¹, *Thomas Yau*², *Chiun Hsu*³,
*Masatoshi Kudo*⁴, *Todd S. Crocenzi*⁵, *Tae-You Kim*⁶,
*Su-Pin Choo*⁷, *Jörg Trojan*⁸, *Tim Meyer*⁹, *Yoon-Koo Kang*¹⁰,
*Jeffrey Anderson*¹¹, *Christine dela Cruz*¹¹, *Lixin Lang*¹¹,
*Jaclyn Neely*¹¹, *Anthony B. El-Khoueiry*¹²

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Background and Objectives: HCC tumors are associated with chronic inflammation that can promote an immunosuppressive environment; anti-PD-1 therapy may counter this inhibition. Nivo, a fully human IgG4 monoclonal antibody PD-1 inhibitor, was initially evaluated in a multiple ascending-dose, phase 1/2 study in pts with advanced HCC; it was well tolerated with antitumor activity in different etiologies, across lines of therapy, justifying an expansion phase. Interim results are presented.

Methods: Pts had histologically confirmed, advanced HCC and Child-Pugh class A. Dose expansion at nivo 3 mg/kg occurred in 4 cohorts: uninfected sorafenib (sor) naïve/intolerant, uninfected sor progressors, HCV-, and HBV-infected. Primary endpoint was confirmed overall response rate (ORR) by RECIST 1.1. Secondary endpoints included OS, PFS, time to progression, and biomarker assessment.

Results: Dose expansion enrolled 206 pts; 75% had extrahepatic metastasis, 7% vascular invasion, and 64% prior sor. Across cohorts, pts received a median of 5–6 doses (range: 1–19). Treatment-related AEs (TRAEs) occurred in 104 pts (50%); the most frequent were fatigue (17%) and pruritus (12%). Grade 3/4 TRAEs were seen in 28 pts (14%); most common were ALT and AST increases (3% each). 68 of 174 evaluable pts (39%) had a decline in tumor burden. Preliminarily, 91 pts (55%) had ≥18 wks follow-up and/or PD. ORR for these pts was 9% (8/91) [14% (3/22) uninfected sor naïve/intolerant; 7% (2/27) uninfected sor progressors; 14% (3/21) HCV-infected; (0/21) HBV-infected]. 6 mos OS rate was 69% (95% CI, 0.43–0.85). Responses were observed in pts with and without quantifiable PD-L1 measured by IHC. Antiviral responses in HCV- and HBV-infected pts have been

observed as measured by declines in HCV RNA and quantitative HBV surface antigen.

Conclusions: AEs were consistent across nivo cohorts and similar to profiles in other tumor types. Results are preliminary and may underestimate response; data indicate activity across all etiologic subtypes and lines of therapy, supporting ongoing study of nivo in HCC.

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Clinical Trial Registration Number: NCT01658878.

0098

Radiotherapeutic Strategies for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis in a Hepatitis B Endemic Area

Jung Ho Im¹, Sang Min Yoon², Hee Chul Park^{3,13}, Jong Hoon Kim², Jeong Il Yu^{3,13}, Tae Hyun Kim⁴, Jun Won Kim⁵, Taek-Keun Nam⁶, Kyubo Kim⁷, Hong Seok Jang⁸, Jin Hee Kim⁹, Mi-Sook Kim¹⁰, Won Sup Yoon¹¹, Inkyung Jung¹², Jinsil Seong¹

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Objectives: This nationwide, multicenter study investigated treatment outcomes as well as the optimal radiotherapeutic strategy in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT).

Methods: We retrospectively reviewed the records of 985 patients who received radiotherapy (RT) for PVTT. The median equivalent RT dose was 48.75 Gy, and combined treatment was administered to 657 patients (66.7%). The PVTT and primary tumor were irradiated in 413 patients (41.9%), and PVTT only was targeted in 572 patients (58.1%).

Results: The response rate of the PVTT was 51.8%, and RT responders had a significantly longer survival than non-responders (15.2 months vs. 6.9 months). Equivalent RT dose and combined treatment predicted response of PVTT by multiple logistic regression. The median overall survival (OS) was 10.2 months. Multivariate analysis revealed the equivalent RT dose >45 Gy and combined treatment as significant positive factors for OS. In the propensity score matching analysis, the combined treatment group had better OS than the no combined treatment group, while the OS of the PVTT + primary tumor group did not differ significantly from that of the PVTT only group.

Conclusions: The equivalent RT dose >45 Gy, given in combination with other treatments, provided better PVTT control and OS. The optimal RT volume is suggested for either PVTT + primary or PVTT only. Taken together, multimodal treatment with equivalent RT dose higher than 45 Gy is recommended for patients with HCC and PVTT.

Session 18: Oral Presentation (Surgery and Radiology)

0027

Pre-Operative Anaemia – Common and Prognostic for Hepatocellular Carcinoma Treated by Hepatectomy

Kevin Ka Wan Chu, Kenneth Siu Ho Chok, Albert Chan, Tan-To Cheung, Chung-Mau Mau, Ronnie Poon
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Objective: Hepatocellular carcinoma is one of the commonest cancer while liver resection is the main curative treatment for hepatocellular carcinoma. At the same time, anaemia is common in cancer patients. Although the prognostic value of anaemia was shown in other cancers, its role in hepatocellular carcinoma was not clear. We evaluated the prevalence of anaemia in patients underwent hepatectomy and the prognostic value of anaemia for these patients.

Methods: The study included 488 patients who underwent liver resection for hepatocellular carcinoma with curative intent between 2002 and 2012. Pre-operative investigation performed on the first consultation were reviewed while anaemia was defined as haemoglobin <13.3 g/dl for man and <11.5 g/dl for women according to our haematology

laboratory. Survival analysis were performed and prognostic factors were identified with cox-proportional hazard models.

Results: The anaemic group consisted of 122 patients while the normal group consisted of 362 patients. The overall median survival for the anaemic group was shorter (53 months vs. 98 months, $p = 0.002$). And the disease free survival for the anaemic group was also poorer ($p = 0.016$). In multi-variable analysis, anaemia was adjusted and AFP >400 ng/ml, blood transfusion, multiple tumours, macrovascular invasion, adjacent organ invasion and microvascular invasion were independent predictive factor for survival.

Conclusion: The current study showed that 25% of hepatectomy candidates had pre-operative anaemia. Anaemia is associated with poorer long term survival with RR 1.48, 95% CI 1.12–1.97, $p = 0.007$.

0113

Development of Cholangiocarcinoma in a Printing Company Employee: Occupational Cholangiocarcinoma

Shoji Kubo¹, Shigekazu Takemura¹, Shogo Tanaka¹, Masahiko Kinoshita¹, Genya Hamano¹, Yasuni Nakanuma², Yasunori Sato³, Sachiyo Mimaki⁴, Kazuya Tsuchihara⁴

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Background: Since the development of cholangiocarcinoma in a printing company employee in Osaka has been reported in 2012, cholangiocarcinoma in 38 patients who had been exposed to high concentration of 1,2-dichloropropane (DCP) and/or dichloromethane (DCM) were classified as an occupational disease by the Japanese government. In 2014, DCP was classified into class 1 (carcinogenic) and DCM was classified into class 2A (probably carcinogenic) by IARC.

Methods: The clinicopathological findings of the patients, especially those in Osaka, and mechanism of carcinogenesis were investigated.

Results: In a printing company in Osaka, cholangiocarcinoma developed in 18 patients in about 100 past or present employee and their age at the time of detection ranged from 25 to 48 years. The patients were exposed to high concentration of DCP and/or DCM for a long term. The serum concentrations of γ -GTP increased in all patients and the increase had been observed several years before the detection of cholangiocarcinoma. On the diagnostic imaging, the regional dilatation of intrahepatic bile ducts without obstruction due to

cholangiocarcinoma was often observed. The primary adenocarcinoma developed mainly at the common hepatic duct or intrahepatic large bile ducts. The main tumors were classified into mass-forming type with or without periductal invasion or intraductal growth type intrahepatic cholangiocarcinoma, and papillary type of extrahepatic cholangiocarcinoma. The precancerous lesions such as biliary intraepithelial neoplasia and intraductal papillary neoplasm of bile duct, and chronic bile duct injury were observed at various parts of the bile ducts. These lesions were positive for H2AX. Whole-exome analysis on 4 patients with such cholangiocarcinoma showed a high mutation burden, strand bias and unique trinucleotide mutational signatures.

Conclusions: Although the exact mechanism of the development of cholangiocarcinoma is still unknown, DCP and DCM induce cholangiocarcinoma through chronic bile duct injury and precancerous lesions cause by DNA injury.

0034

Outcomes of Emergency and Interval Hepatectomy for Ruptured Resectable Hepatocellular Carcinoma: A Single Tertiary Referral Centre Experience

Andrew K.Y. Fung, Charing Chong, Kit Fai Lee, John Wong, Yue Sun Cheung, Kwong Wai Fong, Paul B.S. Lai

Prince of Wales Hospital, Hong Kong

Background and Objectives: Hepatocellular carcinoma (HCC) is the fifth commonest malignancy globally. Rupture HCC is the third commonest presentation of this condition and treatment is determined by the haemodynamic stability of the patient. In the presence of haemodynamic instability, management can include one-stage emergency hepatectomy or initial haemostasis with trans-arterial embolisation (TAE) followed by interval hepatectomy. In this single-centre study, the short and long term outcomes of patients who underwent emergency and interval hepatectomy for ruptured resectable HCC were analysed.

Methods: The clinical data of patients with ruptured HCC presenting between April 2004 and October 2015 to our hospital were collected and analysed retrospectively. Emergency hepatectomy was defined as liver resection within 48 hours of the clinical or radiological diagnosis of HCC rupture. Recurrent HCC was diagnosed with CT or PETCT to identify the location of intra- and extra-hepatic recurrence and tumour disease burden.

Results: Thirty patients underwent hepatectomy for ruptured HCC. Nine (30%) patients underwent emergency hepatectomy. The mean age was 56 and 54 years ($p = 0.13$) with a similar distribution of male patients in both groups (89% vs. 90%, $p = 0.66$). The mean HCC tumour size was

larger (10.5 vs. 8.3 cm, $p = 0.17$) in the emergency group. Total blood loss (3,000 vs. 850 mls, $p = 0.002$) and mean total units of red blood cell transfusion (1.9 vs. 0.5 units, $p = 0.27$) were greater in the emergency group.

The post-operative complication rate was 44% (wound infection $n = 2$, pleural effusion $n = 2$) and 38% (wound infection $n = 2$, pleural effusion $n = 4$, confusion $n = 1$, ascites $n = 1$) in the emergency and interval groups, respectively ($p = 0.53$). One patient in the interval group required pigtail drainage of pleural effusion. The median total length of hospital stay was 10 and 12 days respectively ($p = 0.07$) with no thirty-day mortality in both groups.

The median time to intra-hepatic recurrence was 7.8 and 5.0 months ($p = 0.12$) and extra-hepatic recurrence was 6.8 and 9.7 months ($p = 0.59$) in the emergency and interval groups, respectively. The median time to earliest recurrence was 6.8 and 5.6 months ($p = 0.74$) and median overall survival was 29 and 15.7 months ($p = 0.25$), with survival rates of 78%, 45%, 0% and 85%, 43%, 5% at 1, 3 and 5 years in the emergency and interval groups respectively.

Conclusion: This study showed the feasibility of emergency or interval hepatectomy for highly selected patients with ruptured resectable HCC. The overall survival rates were similar in both groups. Hepatectomy should be considered for ruptured HCC provided the patient could tolerate curative resection.

subjected to MH after excluded those resection less than 3 segments. All relevant clinico-pathological variables were analyzed. Disease free survival (DFS) and overall survival (OS) rates of both groups were compared.

Results: There were no statistically differences between CH and MH groups in pre-operative liver function, prevalence of viral hepatitis, liver cirrhotic, tumor size, histological vascular invasion, blood loss, complication rate and hospital stay. FRLV increased from 31.6% to 57.4% by using CH resection lines. The parenchymal transection time is remarkably longer in CH than MH. The 1, 3 and 5-years RFS rate of CH were 86.7%, 66.7% and 60.0% in respectively, and MH were 77.2%, 57.0% and 50.3% in respectively ($p = 0.580$). The 1, 3 and 5-years OS rate of CH were 100%, 100% and 93.3% in respectively, and MH were 87.6%, 71.9% and 62.6% in respectively ($p = 0.028$). Histological vascular invasion was found to be an independent risk factor of disease recurrence in cox regression model. MH and vascular invasion were independent poor prognostic factors in multivariate analysis of OS.

Conclusions: CH is a relatively time-consuming and technique-demanding procedure, but excellent results could be achieved in experience hands. In those require large volume resection, CH increases liver volume preservation and results in the same disease recurrence as MH. In a high endemic area of hepatitis and cirrhosis, CH should still play an important role in surgical treatment of early stage CL-HCC.

0079

Central Hepatectomy Still Plays an Important Role in Treatment of Early Stage Central-Located Hepatocellular Carcinoma – A Single Center Experience and Management Algorithm

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Background: Management of centrally located hepatocellular carcinoma (CL-HCC) poses a challenge to surgical team especially in cirrhotic patients. Major hepatectomy (MH) is more radical but may compromise on functional remnant liver volume (FRLV). Conversely, central hepatectomy (CH) ensures adequate FRLV but the long term benefits were not clearly demonstrated. In this study, we present our outcomes in management of CL-HCC with an approach of liver preservation.

Methods: Sixty-four consecutive patients with early stage CL-HCC underwent liver resection over a period of 4 years. Fifteen patients underwent CH while other 33 were

0053

Combined Major Liver Resection and Radiofrequency Ablation for Multifocal Hepatocellular Carcinoma

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Background: Multifocal hepatocellular carcinoma (HCC) remained a difficult condition to be treated, as patients may be out of liver transplantation criteria, as well as inadequate liver remnant to undergo major hepatectomy. This study aimed to review the outcome of the patents undergoing combined resection and radiofrequency ablation (RFA).

Methods: From January 2001 to December 2013, the postoperative and oncological outcomes of all patients who had undergone major liver resection and RFA for multifocal HCC in Queen Mary Hospital, Hong Kong, were reviewed. The baseline characteristics was matched by propensity score matching in a ratio of 1:8. Survival analysis was performed by Kaplan Meier methods and compared between subgroup with log-rank test. Risk factors affecting survival were determined by Cox regression model.

Results: A total of 16 patients undergoing major liver resection and RFA for multifocal were matched with 128

patients undergoing major resection alone during the study period. There were no difference in terms of the baseline characteristics, comorbidities. Patients in both groups had similar Child Pugh grading and MELD score. In spite of the higher ICG retention rate at 15 minutes for the combined group, it was still within the normal range (12.7% vs. 10.6%, $p = 0.026$). Both groups of patients suffered from similar number of tumors, but only 47 patients (36.7%) were bilobar in the liver resection group. There were no difference in terms of the operative procedures, outcome and hospital stay, neither the pathology of the tumors. Despite the multifocality of the HCC and bilobar involvement, combined resection resulted in similar overall survival (5-year 24.1% vs. 40.1%, $p = 0.164$). Prolonged hospital stay and tumor with microvascular invasion were the risk factors for poorer overall survival.

Conclusion: Aggressive management of HCC with combination modalities, such as liver resection and RFA, should always be considered for bilobar multifocal HCC.

Session 19: Oral Presentation (Basic Science, Hepatology and Oncology)

0014

Diagnostic Value of Diffusion Kurtosis Imaging and T₁-Mapping on Gd-EOB-DTPA-Enhanced MR Imaging in Assessment of Liver Regeneration after ALPPS

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Background and Objectives: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently been described as a promising strategy to induce a rapid and marked increase in future liver remnant (FLR) volume. Diffusion kurtosis imaging (DKI) and Gd-EOB-DTPA-enhanced MRI with T₁-mapping sequence reflect the states of liver diffusion and hepatocellular function respectively. The objective of our study was to investigate their diagnostic value in assessing liver regeneration and functional compensation after ALPPS.

Methods: Thirty rats were divided into the ALPPS group ($n = 10$), the portal vein ligation (PVL) group ($n = 10$), and the control group ($n = 10$). MRI of the liver including DKI and T₁-mapping on Gd-EOB-DTPA-enhanced MR imaging was performed. Mean apparent diffusion (MD), mean kurtosis (MK), T₁ relaxation time on hepatobiliary phase (HBP), the decrease rate ($\Delta\%$) of the FLR, as well as the MR liver volume

were calculated and compared before and after surgery. Radiologic-pathologic correlation was also assessed.

Results: Mean volume of FLR (the right median lobe) significantly increased after ALPPS (3.376 vs. 9.103 cm³; $t = 12.84$, $P < 0.0001$); volume increase percentage of FLR after ALPPS was higher than PVL ($t = 2.374$, $P = 0.0304$), although the percentage of total liver volume was not significantly different ($t = 0.267$, $P = 0.793$). MD of FLR 7 days after ALPPS was lower than that before surgery ($t = 2.246$, $P = 0.033$), no difference was found in MK ($t = 0.244$, $P = 0.809$). While MK after ALPPS was higher than PVL ($t = 2.961$, $P = 0.008$), but no difference existed in MD ($t = 0.574$, $P = 0.573$). Meanwhile, HBP ($t = 0.624$, $P = 0.544$) and $\Delta\%$ T₁ relaxation time ($t = 0.370$, $P = 0.717$) of FLR showed no differences before and 7 days after ALPPS. HBP T₁ relaxation time after ALPPS was lower than PVL ($t = 3.583$, $P = 0.003$), while $\Delta\%$ T₁ relaxation time was higher ($t = 3.837$, $P = 0.0016$). Microscopy showed the density of hepatocytes in the FLR after both ALPPS and PVL increased compared with preoperation, and the hepatocytes of former were more hypertrophic and denser.

Conclusions: The proliferation of FLR after ALPPS was effective and superior to traditional PVL. DKI and T₁-mapping were useful to evaluate the microstructure of liver regeneration and functional compensation after ALPPS.

0087

Human Amniotic Epithelial Cell Exosomes Reduce Proliferation of Hepatocellular Carcinoma Cell Lines

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Exosomes are important components of tumorigenesis via their modulating effect on the cellular microenvironment and modification of tumour immune responses. Limited studies suggest that exosomes play an important role in the development and progression of HCC.

We aim to assess the impact of Human Amniotic Epithelial cell (hAEC) exosomes on HCC cell lines in vitro and in vivo.

A Transwell method with 1 μm pores was used to allow hAEC exosome diffusion into Huh-7 cell line (representing moderately differentiated HCC), Sk-Hep1 cell line (representing poorly differentiated HCC) and compared with a control arm for all experiments.

Cell proliferation was assessed using Alamar Blue Staining over 4 days. The effect of hAEC on cell motility was assessed via wound healing assay. Immunofluorescence staining for vimentin and EPCAM as markers of epithelial mesenchymal transformation (EMT) were performed.

We treated Nod Scid Gamma (NSG) mice with thioacetamide for 4 months to induce full-fledged cirrhosis.

We injected half a million cells of Huh-7 or Sk-Hep1 cell lines into the spleen of each mouse (3 mice per cell line). We then injected exosomes isolated by centrifuge from hAEC intraperitoneally into each mice daily for 2 weeks, then harvested the livers of the mice. This was compared against control.

The proliferation of Huh-7 was reduced in the hAEC arm compared with control (5842 vs. 9042 units on Alamar Blue Stain). The proliferation of Sk-Hep1 was reduced in the hAEC exosome arm compared with control (2264 vs. 3113). The wound healing assay demonstrated reduced cell motility in the hAEC arm compared to control for Huh-7 (67.0% vs. 82.1% healing). Wound healing was also reduced in the hAEC arm vs. control in Sk-Hep1 (51.5% vs. 70.1%). Immunofluorescence staining for both vimentin and EPCAM were reduced in Huh-7 and Sk-Hep1 cells treated with hAEC exosomes as compared to control. Upon harvesting of the mice, there was an average of 1 Huh-7 colony per slide for the hAEC arm, compared with an average of 7.7 colonies for the control arm. Sk-Hep1 was diffuse and infiltrative and did not form clear borders. There was less tumour burden in the hAEC exosome arm compared with control.

hAEC exosomes have the potential to retard proliferation and motility, both in vitro and in vivo. The ability to define and harness exosomes has tremendous potential for the treatment of HCC.

0111

Phase 1/2 Safety and Antitumor Activity of Nivolumab (Nivo) in Patients (pts) with Advanced Hepatocellular Carcinoma (HCC): Interim Analysis of the CheckMate-040 Dose Escalation Study

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Background and Objectives: For pts with advanced HCC on sorafenib (sor), overall survival (OS) is 11 mo; median OS with best supportive care (BSC) post-sor failure is 7–8 mo. Safety and preliminary antitumor efficacy of nivo, a fully

human IgG4 mAb PD-1 inhibitor, was evaluated in a multiple ascending-dose, phase 1/2 study in pts with advanced HCC with clinical follow-up to 3 yrs.

Methods: Pts had histologically-confirmed, advanced HCC, Child-Pugh (CP) score ≤ 7 , and previously failed, refused, or were intolerant of sor. Dose escalation occurred in 3 parallel cohorts by etiology: no active hepatitis virus infection, HBV-infection, or HCV-infection. Pts received nivo 0.1–10 mg/kg for up to 2 yrs. The primary endpoint was safety. Secondary endpoints included antitumor activity by RECIST1.1 and DOR; exploratory endpoints included biomarker assessment.

Results: 51 pts were enrolled and treated with nivo: baseline CP scores were 5 (n = 44) or 6 (n = 7), 76% had extrahepatic metastasis, 12% had vascular invasion, and 73% had prior sor. 10 pts remain on study; 41 discontinued, most (n = 35) due to PD and 1 due to a treatment-related adverse event (TRAE) of ALT and AST increase. TRAEs occurred in 39 pts (77%); most common were rash and AST increase (20% each). Grade 3–4 TRAEs were seen in 10 pts (20%); most common were AST increase (10%), lipase and ALT increase (6% each). A maximum tolerated dose was not reached. 48 pts were evaluable for response. Responses were observed in pts with and without quantifiable PD-L1 as assessed by IHC. Antiviral responses in HCV-infected pts have been observed. Efficacy data are reported as below.

ORR, n (%): 7 (15)

• CR, n (%): 3 (6)

• PR, n (%): 4 (8)

• SD, n (%): 24 (50)

• PD, n (%): 15 (31)

• Not evaluable: 2 (4)

Median DOR, months: 23.7

Pts with decline in tumor burden from baseline, n (%): 17 (37)

Median OS, ^a (95% CI), mo: 15.1 (9.6, 28.6)

OS Rate, ^a %:

• 6 months: 67

• 9 months: 67

• 12 months: 59

• 18 months: 48

^aBased on entire pt population.

Conclusions: Nivo was well tolerated with a manageable safety profile. Treatment produced durable responses and disease stabilization across all dose levels and cohorts. Reported OS rates were favorable relative to historical data for BSC.

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Poster Sessions

Basic Science and Pathology

0005

A Combination Treatment of Glycolytic Inhibitor and Reactive Oxygen Stress Enhancer in Sorafenib-Resistant and High Metastatic Potential Hepatocellular Carcinoma Cells

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Background and Aims: Acquisition of anoikis resistance (AR) is a prerequisite for the metastasis in hepatocellular carcinoma (HCC). However, little is known about how energy metabolism and antioxidant system are changed in HCC AR cells. We aimed to evaluate the anti-tumor effect of a combination treatment of 3-bromopyruvate (3-BP), an inhibitor for glycolysis, and buthionine sulfoximine (BSO), an inhibitor for glutathione synthesis in HCC AR cells.

Methods: We compared glycolysis, reactive oxygen species (ROS) production, and chemoresistance between Huh-BAT, HepG2 human HCC cells and corresponding AR cells such as Huh-BAT AR and HepG2 AR cells. Expression of hexokinase II, gamma-glutamylcystine synthetase (rGCS), and epithelial-mesenchymal transition markers such as E-cadherin and Snail in AR cells was compared to Huh-BAT and HepG2 cells. Lactic acid and ROS production, and invasion capability were assessed in AR cells when treated with 3-BP, BSO and a combined treatment. Anti-tumor effect of a combination treatment of 3-BP and BSO were evaluated in AR cells and HCC xenograft mouse model using TUNEL assay.

Results: HCC AR cells showed a significantly higher chemoresistance, metastatic potential, glycolysis, and lower ROS production than Huh-BAT and HepG2 cells. Expression of hexokinase II, rGCS, and Snail was higher in AR cells than Huh-BAT and HepG2 cells. A combination treatment of 3-BP and BSO effectively suppressed AR cell growth through apoptosis by blocking glycolysis and enhancing ROS levels, and significantly inhibited invasion capability of AR cells as compared to each treatment. In a xenograft mouse model, tumors induced from AR cell more rapidly grew than attached

cells. Tumor growth from AR cells was significantly suppressed in the group treated with 3-BP and BSO as compared to the group treated with 3-BP, or sorafenib alone.

Conclusions: These results demonstrate that a combination treatment of 3-BP and BSO has a synergistic anti-tumor effect in HCC AR model. This strategy might be an effective adjuvant therapy to patients with sorafenib-resistant HCC.

0009

Assessment of mTOR Activation in Egyptian Patients with Hepatocellular Carcinoma

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Background and Aim: Hepatoceular carcinoma (HCC) is one the most common primary tumor in Egypt. Currently, the therapeutic options for advanced tumors are limited with only one agent, Sorafenib, showing significant short-term clinical efficacy. Identification of additional therapeutic agents is crucial for improvement of survival. A recent small phase 1/2 clinical trial has suggested that tumor phospho-mTOR (pm-TOR) expression could predict patient's response to the selective mTOR inhibitor temsirolimus. The aim of this study was to determine the frequency of alteration in pmTOR in Egyptian patients with HCC and to explore potential mechanisms for resistance for this agent in HCC cell lines.

Materials and Methods: Phospho-mTOR was studied using immunohistochemistry in unselected sporadic HCC Egyptian patients. The expression of the upstream regulator, PTEN, was also assessed in a subset of tumors. In-vitro cell survival assay was used to investigate the therapeutic efficiency of temsirolimus in correlation with the expression of mTOR/PTEN in HCC cell lines.

Results: Out of the 123 tumors assessed strong uniform expression of pmTOR was identified in 12 (9.8%), moderate or heterogenous strong expression in 29 (23.6%), weak expression in 44 (35.8%) and no expression in 38 (30.9%). No

correlation between PTEN and pmTOR expressions was observed in 37 tumors where both were assessed. In-vitro studies suggested that tolerated therapeutic levels of temsirolimus cause partial suppression of cellular growth rather than cell death/apoptosis.

Conclusion: Our results suggest that only a small subset of HCC patients show strong uniform activation of the mTOR pathway suggesting that these will be the best candidates for targeted therapy using this agent. It is essential before starting targeted based therapy to obtain biopsy from the patients in order to better select patient population responsive to therapy.

0026

Tumor Angiogenesis Associated Gene Profiling of Dickkopf-1 Stimulated HUVECs

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Background and Aim: Tumor angiogenesis is essential for invasive tumor growth and metastasis. Dickkopf (DKK)-1, an antagonist of Wnt signal, participates in tumor development and progression. This study evaluated whether DKK-1 stimulation increases gene activation of angiogenesis and endothelial mesenchymal transition (EnMT).

Methods: Human umbilical vein endothelial cells (HUVECs) were stimulated with recombinant DKK-1 or concentrated conditioned medium from DKK-1-transfected 293 cells. Following stimulation, the analysis of DKK-1 stimulated variable genes, such as angiogenesis, EnMT, proliferation was examined by RNAseq assays. In addition, the PPI (protein-protein interaction) of DKK-1 stimulated endothelial cell on angiogenesis and EnMT were assessed by cytoscape and DAVID bioinformatics analysis.

Results: The results of the RNAseq indicated that 49 genes were up-regulated and 684 genes were down-regulated in the HUVECs. Certain genes that may be significant in the regulation of HUVECs were identified. Up-regulated genes almost related angiogenesis, EnMT, Proliferation and cell structure related genes. Down-regulated genes related cell cycle inhibition and apoptosis.

Conclusion: These results may aid the studying of the mechanisms through which DKK-1 stimulated HUVECs acquire their distinctive properties. Modulation of DKK-1 may shed light on development of novel strategies to control tumor angiogenesis and metastasis.

0077

Serum Exosomal MicroRNAs as Potential Biomarker for HBV-Related Hepatocellular Carcinoma

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Background and Objectives: Recent studies have shown that circulating microRNA (miRNA) is a potential biomarker in various types of malignancies including hepatocellular carcinoma (HCC). Exosomes are small vesicles released by various cell types including cancer cells into the extracellular space. Tumor-derived exosomes contain numerous functional microRNAs (miRNAs), which could represent tumor biology as a liquid biopsy. We previously reported that there was a significant difference in the levels of several serum exosomal miRNAs in patients with HBV-related HCC compared with those with chronic hepatitis B (CHB) or liver cirrhosis (LC) (Sohn W et al, Exp Mol Med 2015;47:e184). The aim of our study was to identify potential serum exosomal miRNA biomarker for HBV-related HCC using miRNA array.

Methods: We performed the miRNA expression profiling in isolated serum exosomes in patients with HBV-related HCC (n = 6) and patients with CHB (n = 5). Exosomal microRNA was extracted from 500 µl of serum using the SeraMir Exosome RNA Isolation kit according to the manufacturer's instruction. Exosomal microRNA profiling was performed using nCounter Human miRNA Expression Assay kit V3. nSolver Analysis software V3.0 (NanoString) was used for data analysis.

Results: When we identify exosomal miRNA that expressed at least 1.5 fold higher or lower between HBV-related HCC and CHB, a total of 5 miRNAs (hsa-miR-150-5p, hsa-miR-342-3p, hsa-miR-16-5p, hsa-miR-26b-5p, and hsa-miR-22-3p) were significantly downregulated in HCC patients compared to CHB. In contrast, there was no exosomal miRNA that was significantly upregulated in HCC compared to CHB. When we reviewed published literatures, it was reported that miR-150-5p was down-regulated in HCC tissue compared with non-tumor tissue, and miR-150-5p suppressed cancer cell migration and invasion (Li T et al, PLOS One 2014;30:e115577). The overexpression of miR-342-3p inhibited HCC proliferation (Zhao L et al, Biochem Biophys Res Commun 2015;457:370–7). miR-26b-5p suppresses epithelial-mesenchymal transition, migration and invasion by targeting SMAD1 in HCC (Wang Y, et al, Oncotarget 2016, e-pub). miR-22 was downregulated in HCC tissues and miR-22 has an antiproliferative effect on HCC cells by targeting histone deacetylase 4 (Zhang J et al, Br J Cancer 2010;103:1215–20).

Conclusions: Our study identified several exosomal miRNA signatures downregulated in HBV-related HCC using

nCounter human miRNA profiling platform. Serum exosomal microRNA profiling may be used as a useful liquid biopsy to detect novel biomarkers for HCC.

Hepatology

0011

Serpin Peptidase Inhibitor (*SERPINB5*) Genetic Polymorphisms Are Associated with Susceptibility to Hepatocellular Carcinoma

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Background and Objectives: Hepatocellular carcinoma (HCC) represents the second leading cause of cancer-related death worldwide. The serpin peptidase inhibitor *SERPINB5* is a tumour-suppressor gene that promotes the development of various cancers in humans. However, whether *SERPINB5* gene variants interfere with gene regulation or protein structure or play a role in cancer susceptibility remains unknown.

Methods: In this study, we genotyped 6 single-nucleotide polymorphism (SNP) tags of the *SERPINB5* gene in an independent cohort from a replicate population comprising 305 cases and 590 controls.

Results: Patients who had at least one rs2289520 C allele in *SERPINB5* tended to exhibit better liver function than patients with genotype GG (Child-Pugh grade A vs. B or C; $P = 0.047$). Next, haplotype blocks were reconstructed according to the linkage disequilibrium structure of the *SERPINB5* gene. A haplotype 'C-C-C' (rs17071138 + rs3744941 + s8089204) in block 1 of *SERPINB5*-correlated promoter SNPs showed a significant association with an increased HCC risk [adjusted odds ratio (AOR)=1.450; $P = 0.031$]. Haplotypes 'T-C-A' and 'C-C-C' (rs2289519 + rs2289520 + rs1455555) in block 2 located in the *SERPINB5* coding region had a decreased (AOR = 0.744; $P = 0.031$) and increased (AOR = 1.981; $P = 0.001$) HCC risk, respectively. Finally, an additional integrated *in silico* analysis confirmed that these SNPs affected *SERPINB5* expression and protein stability, which significantly correlated with tumour expression and subsequently with tumour development and aggressiveness.

Conclusions: Taken together, our data suggest that genetic variants of *SERPINB5* contribute to the occurrence of liver cancer. The findings regarding these biomarkers provide a prediction model for risk assessment.

0017

Assessment of Risk for Recurrence of Hepatocellular Carcinoma: An Extended Surveillance Interval 1 Year after Curative Treatment

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Background/Aims: The guidelines recommend surveillance for hepatocellular carcinoma recurrence be performed 3-monthly during 1 year after curative treatment, and 6-monthly thereafter in all patients. This strategy did not reflect individual risk based on patients' tumor biology. We aimed to identify patients who can extend surveillance intervals 1 year after treatments.

Methods: We retrospectively analyzed 1,490 patients treated with hepatectomy/radiofrequency ablation in the Barcelona Clinic Liver Cancer stage 0/A and well-preserved liver function. In patients under 3-monthly surveillance in total periods, a new model for survival was developed using multivariable analysis: the derivation ($n = 682$)/validation set ($n = 341$). Survival rates in low-risk patients by the new model were compared according to surveillance intervals 1 year after treatments: 3-monthly vs. 6-monthly ($n = 467$) after propensity score matching and lead time bias correction.

Results: Albumin levels, MELD score, tumor size, alpha-fetoprotein levels, and 1-year recurrence were independent factors for survival: odds ratios (OR) of 0.33, 1.12, 1.06, 1.09, and 6.99 respectively (all $P < 0.01$). One-year recurrence showed significantly higher OR than other durations (1–2, 2–3, and >3 years, $P < 0.01$). A new model showed AUROC of 0.81 (the derivation set) and 0.77 (the validation set). Survival rates in low-risk patients of the new model under 3-monthly surveillance 1 year after treatments were not superior to those under 6-monthly surveillance ($P = 0.958$).

Conclusions: Surveillance interval 1 year after treatments in patients with favorable tumor biology can be extended to 6-monthly interval. Surveillance schedules can be optimized to reduce radiation hazard and cost without compromising benefits in low-risk patients.

0025

Partial Splenic Embolization with Transcatheter Arterial Chemoembolization (TACE) in Patients with Hepatocellular Carcinoma Accompanied by Thrombocytopenia: Change of Platelet Count after TACE for 2 Years Compared to the Control Group

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Objectives: 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 and platelet changes with transcatheter arterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) accompanied by thrombocytopenia.

Methods: Twenty HCC with cirrhotic patients were treated with TACE and PSE due to severe thrombocytopenia (platelet count $<45 \times 10^3/\text{mm}^3$). Twenty 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 platelet value after PSE was significantly increased at 12 months ($p = 0.001$). The average platelet count of PSE-TACE group was $38.9 \times 10^3/\text{mm}^3$, $107.9 \times 10^3/\text{mm}^3$, $92.5 \times 10^3/\text{mm}^3$, $93.1 \times 10^3/\text{mm}^3$, $98 \times 10^3/\text{mm}^3$ each other at baseline, 6 months, 1 year, 1.5 year and 2 years after TACE. The average platelet count of control group was $56.8 \times 10^3/\text{mm}^3$, $57.4 \times 10^3/\text{mm}^3$, $58.9 \times 10^3/\text{mm}^3$, $70 \times 10^3/\text{mm}^3$, $56.4 \times 10^3/\text{mm}^3$ each other at baseline, 6 months, 1 year, 1.5 year and 2 years after TACE. The causes of HCC with cirrhosis were similar in both groups ($p = 0.326$). Even though platelet counts of PSE-TACE group was lower than the control group's one, platelet count of PSE-TACE group was elevated until 2 years after TACE. But it was nearly not changed in the control group. The CTP and MELD score were similar between groups after PSE.

Conclusions: PSE with TACE proved to be effective at maintained platelet count after TACE for 2 years compared to control group for treating thrombocytopenia in patient with hypersplenism and HCC. Liver function and Child-Pugh score after PSE was similar with non-PSE patients at 2 years, concurrent PSE with TACE for HCC can maintain hepatic functional reserve. PSE may be considered to patients of HCC with thrombocytopenia before TACE.

0030

Persistent High Serum AFP Can Precede the Detection of Hepatocellular Carcinoma for a Long Time

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Ms. Au KM was a 38 year old woman. She had an old history of pulmonary tuberculosis resulting left destroyed lung. She also had problem of poorly controlled asthma.

She was known to be hepatitis B surface antigen positive during antenatal check-up.

During antenatal follow up, she was found to have deranged liver function test. The serum alanine transaminase level was peak at 1331 IU/L. The serum HBV DNA level was high, 1.09×10^6 IU/ml. Serum Alpha fetoprotein (AFP) was high, 174 ng/ml. However, she refused any antiviral agent at that juncture.

Unfortunately, her pregnancy was complicated by HELLP syndrome and intrauterine growth retardation at week 34. Emergency Cesarean section was performed. Baby girl was given birth uneventfully. She did not have any neurological structural defect.

Ms. Au's liver function test was then gradually improved. However, her serum AFP level was persistently increasing despite normal liver function test. Computer tomography (CT) of abdomen and pelvis did not detect any hepatic lesion and radiological signs of cirrhosis. Positron emission tomography (PET) of whole body did not show any signal of germ cell tumor.

She remained asymptomatic despite progressively elevated serum AFP level. Her serum AFP level reached a plateau at 970 ng/ml. PET scan were repeated serially at 6 months interval in order to follow up for persistent high serum AFP.

The third PET scan finally detected hepatic lesion of suspicious signal at the time of 18 months having persistent elevated serum AFP. This hepatic lesion was arterially enhanced and washed out at portal venous phase at the follow up CT scan. It was likely to be hepatocellular carcinoma, but not germ cell tumor.

Patient was not fit for hepatectomy because of her poor lung function. She was treated by trans-arterial chemoembolization.

Conclusion: Persistent elevation of serum AFP could precede the detection of hepatocellular carcinoma for a long time. Serial imaging is necessary for undiagnosed elevation of serum AFP.

0037

The Diagnostic Values and Influencing Factors of Serum Alpha-Fetoprotein for Hepatocellular Carcinoma in Hepatitis C Virus Related Cirrhosis*June Sung Lee, Kyung-Ah Kim, Jong Yeon Kim, Nam-Hoon Kim, Won Ki Bae*

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Objectives: Serum a-fetoprotein (AFP) is frequently used for the diagnosis of hepatocellular carcinoma (HCC). Most available data concerning AFP come from studies of patients with chronic hepatitis B or other chronic liver disease of mixed etiologies. Studies concerning the diagnostic value of AFP for hepatitis C virus (HCV)-related liver cirrhosis (LC) were limited and the results are conflicting. We evaluated the diagnostic value of serum AFP for the diagnosis of HCC in HCV LC.

Methods: We enrolled in a case-control study 55 HCV HCC and 62 HCV LC patients. We calculated the sensitivity and specificity and analyzed the clinical and biochemical factors influencing the serum AFP levels.

Results: The sensitivities and specificities of serum AFP for the diagnosis of HCC in HCV-related LC were 72.7% and 59.7% for AFP ≥ 20 ng/ml, and 47.3% and 92.5% for AFP ≥ 100 ng/ml respectively. Elevated serum AST was independently associated with elevated serum AFP level in HCV-related LC. In case with AST $\leq 2 \times$ ULN, the specificity of AFP ≥ 100 ng/ml for the diagnosis of HCC was 100%. But in case with AST $> 2 \times$ ULN, the specificity was 83.5% for AFP ≥ 100 ng/ml and 95.0% for AFP ≥ 200 ng/ml.

Conclusions: Serum AST levels influenced the serum AFP level in HCV-related LC. In case with AST $\leq 2 \times$ ULN, AFP greater than 100 ng/ml highly indicates HCC in HCV-related LC, but in case with AST $> 2 \times$ ULN, the specificity of AFP is decreased.

0038

Role of Shear Wave Elastography in Evaluating the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B*Jae Yoon Jeong¹, Joo Hyun Sohn¹, Won Sohn², Tae Yeob Kim¹, Dae Won Jun³, Yongsoo Kim⁴, Woo Kyoung Jeong⁵*

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Objectives: Evaluation of advanced fibrosis and cirrhosis in patients with chronic hepatitis B (CHB) is important for predicting hepatic complications such as hepatocellular carcinoma (HCC). Two-dimensional real-time shear wave elastography (SWE) has been recently introduced and is useful for accurately assessing the extent of liver fibrosis, particularly advanced fibrosis and cirrhosis. This study aimed to investigate the use of measurements of liver stiffness (LS) by SWE for predicting the development of HCC in patients with HBV-related chronic hepatitis or compensated cirrhosis.

Method: We retrospectively collected data on 291 enrolled patients with CHB whose LS was measured by SWE between January 2011 and December 2012. Most patients were treated with oral antiviral agents for various durations. To estimate independent risk factors for HCC development, univariate and multivariate Cox regression analyses were used. The cumulative incidence rates of HCC were calculated by the Kaplan-Meier method.

Results: The mean age of the patients was 46.8 years, with males predominant (67%), and 40 (14%) of the patients had clinical cirrhosis. The median value of LS was 7.4 kPa, and the median follow-up period was 35.8 month (range 3.0–52.8) (784.9 person-years of follow-up). During follow-up, HCC developed in 13 (4.5%) patients, and the cumulative incidence rates of HCC at 1-, 2-, and 4-years were 1.1%, 3.6%, and 8.4%, respectively. On univariate analysis, HCC development was significantly associated with older age (≥ 50 years) (hazard ratio [HR] 5.39, $p = 0.010$), clinical cirrhosis (HR 4.76, $p = 0.005$), lower platelet count ($< 150 \times 10^3/\text{mm}^2$) (HR 3.15, $p = 0.044$), higher total bilirubin (≥ 1.0 mg/dl) and higher LS value (≥ 10 kPa) (HR 5.97, $p = 0.003$). On multivariable analysis, older age (≥ 50 years) and higher LS value (≥ 10 kPa) were independently associated with the risk of developing HCC (HR 4.33, $p = 0.027$ and HR 4.90, $p = 0.009$). The cumulative incidence rate of HCC was significantly higher in patients with

higher LS values (≥ 10 kPa) than those with lower LS values (< 10 kPa) (log-rank test, $p = 0.001$).

Conclusions: Increased LS measured by SWE at any time is associated with an increased risk that patients with CHB will develop HCC. We believe that SWE has an important role in evaluating the risk of HCC development in patients with CHB.

0039

Association of microRNA Machinery Genes with Hepatocellular Carcinoma in a Korean Population

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Background/Aims: Single-nucleotide polymorphisms (SNPs) in microRNA machinery genes might affect microRNA processing and subsequently impact tumorigenesis. The aim of this study was to investigate the associations between SNPs in microRNA machinery genes and hepatocellular carcinoma (HCC) in a Korean population.

Methods: Genotyping of six SNPs in microRNA machinery genes was performed using blood samples from 147 patients with HCC and 209 healthy control subjects.

Results: None of the six SNPs in microRNA machinery genes were significantly associated with HCC development. However, among the models for six polymorphic loci-*DICER* (rs3742330 and rs13078), *DROSHA* (rs10719 and rs6877842), *RAN* (rs14035) and *XPO5* (rs11077)-one allele combination (A-A-T-C-C-C) showed synergistic effects in terms of an increased risk of HCC development (odds ratio = 8.881, 95% confidence interval [CI]=1.889–41.750; $P = 0.002$). Multivariate Cox proportional hazard regression analysis showed a significant survival benefit for the *DICER* rs3742330 GG compared with the AA genotype (hazard ratio [HR], 0.352; 95% CI, 0.155–0.796; $P = 0.013$) and for the *RAN* rs14035 CT compared with the CC genotype (HR, 0.599; 95% CI, 0.363–0.988; $P = 0.046$).

Conclusions: Although we found no direct association between *DICER* (rs3742330 and rs13078), *DROSHA* (rs10719 and rs6877842), *RAN* (rs14035) or *XPO5* (rs11077) polymorphisms and HCC risk, we demonstrated that *DICER* (rs3742330) and *RAN* (rs14035) were associated with the survival of HCC patients. Future studies with larger samples are needed to determine the associations of SNPs in microRNA machinery genes with HCC risk and prognosis.

0044

A Case of Diffuse Infiltrative Primary Hepatic Angiosarcoma Diagnosed by Transjugular Liver Biopsy

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In adults, primary tumors of the liver arising from the vascular elements of mesenchymal tissues include hemangioma and rare malignant tumors such as epithelioid hemangioma or angiosarcoma. Although these tumors appear usually as solitary or multiple nodules, they rarely present with diffuse nodular lesions. Here, we report a case of primary hepatic angiosarcoma in whom diffuse infiltrative lesions were diagnosed by transjugular liver biopsy.

A 60-year-old woman with a history of hypertension visited emergency department complaining of pitting edema and abdominal discomfort. The laboratory examination showed anemia (hemoglobin 9.7 g/dl), mild elevation of alkaline phosphatase 311 U/L, gamma-glutamyltransferase 173 U/L, total bilirubin 1.92 mg/dl, and prothrombin time (INR) 1.38. Echocardiography showed normal ejection fraction and no chamber enlargement. Liver dynamic computed tomography (CT) showed multifocal high-density irregular lesions scattered on precontrast image, which were enhanced on delayed image. Liver dynamic magnetic resonance imaging (MRI) showed diffuse infiltrative arterial enhancing masses with gradual centripetal enhancement involving both hemilivers, suggesting diffuse hepatic hemangiomas or epithelioid hemangioma and angiosarcoma. Initial transjugular liver biopsy yielded insufficient specimen for proper histopathologic diagnosis. She complained of right flank pain 9 days after liver biopsy. Her blood pressure was 88/56 mm Hg and hemoglobin was 6.6 g/dl. Spontaneous rupture and hemoperitoneum was detected on the follow up CT scan. Emergent hepatic artery embolization was performed. In consideration of liver transplantation for the curative treatment, repeat transjugular liver biopsy was performed to exclude malignancy. Pathologic examination showed malignant vascular tumors, consistent with angiosarcoma. Twenty four days following repeat liver biopsy, the patient expired due to progressive hepatic failure.

0050

Validation of the MORE Score Model Predicting Survival of Patients with Recurrent or Progressive Hepatocellular Carcinoma*Sang Il Choi¹, Joong-Won Park¹, Bo Hyun Kim¹, Yoosun Choi², Byung-Ho Nam²*

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Objectives: There has been no prognostic model to evaluate the survival of patients with hepatocellular carcinoma who experience disease recurrence or progression after initial treatment. A model predicting survival of patients with recurrent or progressive hepatocellular carcinoma (MORE score) has recently been developed using clinical parameters, tumor characteristics, initial treatment modality, and response to treatment, and was validated in a single patient cohort. We tried to evaluate the performance of this novel model by applying it to a different prospectively collected patient cohort.

Methods: Of 1,010 patients who were newly diagnosed with and who had undergone initial treatment for hepatocellular carcinoma at the National Cancer Center, Korea, between January 2010 and December 2013, 460 had documented disease recurrence or progression. Clinical data at the time of recurrence or progression were collected and reviewed. A newly developed prognostic model, the MORE score, was used to calculate the survival probabilities of these patients at the time of recurrence or disease progression, and its performance was evaluated using C-statistics for discrimination ability and χ^2 statistics for fitting ability.

Results: The median age was 58.5 years (range, 17–84 years), and the predominant etiology for hepatocellular carcinoma was hepatitis B virus infection (74.3%). The most commonly used initial treatment was chemo-embolization (64.6%), followed by resection (19.6%). The median time to progression after initial treatment was 4.9 months. C-statistics of the MORE score for 1-, 3-, and 5-year survival were 0.892 (95% confidence interval: 0.865–0.919), 0.842 (0.816–0.868) and 0.829 (0.824–0.854) respectively; χ^2 statistics showed corresponding values of 9.651, 17.170, and 19.629 for 1-, 3-, and 5-year survival.

Conclusions: The MORE score was validated using a different patient cohort that was collected prospectively. The model showed excellent discrimination ability and correctly predicted the survival of the patients, especially at 1 year. This novel model should be useful in real-world clinical practice in communicating with patients and planning subsequent treatment.

0054

Hepatocellular Carcinoma in Pathological Non-Cirrhosis: An Etiology-Based Characteristics and Occult Hepatitis B Virus (HBV) Infection in an HBV-Endemic Area*Chang Woo Shim, Joong-Won Park, So Hee Kim, Jin Sook Kim, Sook-Kyung Lee, Bo Hyun Kim, Sung Hoon Kim, Eun Kyung Hong*

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Background: Although hepatocellular carcinoma (HCC) usually develops in cirrhotic liver, a significant proportion of HCC also develops in the absence of cirrhosis. We identified the etiology-based clinicopathological features of HCC in non-cirrhotic liver in Korea, a hepatitis B virus (HBV)-endemic area.

Method: Of a cohort of 2,876 patients first diagnosed and treated at the National Cancer Center, Korea, between 2000 and 2009, 710 HCC patients with resection or transplantation were enrolled. Cirrhosis was diagnosed by pathology.

Result: Of 710 patients, the median age was 54 years. 86% had modified Union for International Cancer Control (mUICC) stage I or II disease and 96.1% had Child-Pugh class A liver function, and 178 (25%) did not have cirrhosis (NCL group). The median overall survival (OS) was no statistically significant difference in between the NCL and liver cirrhosis (LC) groups.

The main cause of HCC was hepatitis B virus (HBV) infection (77.2%), followed by cryptogenic disease (11.0%). According to etiology, HCC patients with HBV, HCV, alcoholic, and cryptogenic disease did not have cirrhosis in 19.2%, 32.5%, 50.0%, and 48.7% of cases, respectively. Compared to the LC group, the NCL group was significantly more likely to be older, and have a larger tumor size, smaller tumor number, lower mUICC stage and more non-HBV etiologies.

The anti-HBV core positivity in the non-HBV cases and HBV DNA positivity in the liver (occult HBV infection; OBI) of the non-HBV cases was 82.2%, 45.0% in the NCL group, and 78.7%, 40.0% in the LC group, respectively. ($p > 0.05$) In the NCL group, non-HBV HCC patients had no or lower fibrosis stage comparing to HBV HCC patients but there was no difference in survival; OBI did not increase the METAVIR stage.

Conclusion: In patients with alcoholic HCC or cryptogenic HCC, half had non-cirrhotic liver and almost half had OBI. One-third of HCV HCC had non-cirrhotic liver, and there was no OBI. OBI did not increase fibrosis stage. This study may be helpful for understanding the fibrosis status and OBI of HCC patients in an HBV-endemic area.

0056

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

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

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

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

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

0057

Evaluation of Liver Stiffness in Sorafenib-Treated Patients with Advanced HCC*Ming-Chin Yu¹, Chien-Fu Hung², Tsung-Han Wu¹, Chao-Wei Lee¹, Kuang-Tse Pan², Yi-Cheng Chen³*¹Department Surgery Chang-Gung Memorial Hospital, Taoyuan, ²Department Radiology Chang-Gung Memorial Hospital, Taoyuan, ³Department Gastroenterology Hepatology, Taoyuan, Taiwan

Sorafenib is a multi-tyrosine kinase inhibitor and the standard therapy for advanced hepatocellular carcinoma (HCC). This retrospective observational study aimed to explore the anti-fibrotic effect of sorafenib in patients with advanced HCC by measuring the shear wave velocity (SWV) using ARFI elastography.

Seventeen consecutive patients with advanced HCC were recruited from May 2014 to July 2015. The daily dose of sorafenib was 400–800 mg. SWV measurements and measurements of noninvasive serum markers for liver fibrosis, such as the aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR), the AST to platelet ratio index (APRI), the fibrosis-4 index (FIB-4) and the Lok index, were recorded at the beginning of sorafenib treatment and 3–6 months after sorafenib treatment. The treatment response was evaluated via computed tomography after each cycle of sorafenib therapy. A paired comparison of variables at different time points was performed using a paired t test.

The mean age was 59.7 years, and 14 (82.4%) males were included. The mean duration of sorafenib treatment was 11.1 months, and the mean survival time until the last visit was 15.1 months. Two patients achieved a complete response, 1 patient achieved a partial response, 6 patients had stable disease and 8 patients had progressive disease. The mean SWV decreased from 2.37 m/sec at the beginning of sorafenib treatment to 1.90 m/sec 3 months after sorafenib treatment ($p < 0.01$). This trend was observed in patients with and without liver cirrhosis (reduction from 2.49 to 2.06 m/sec, $p = 0.06$, and reduction from 2.32 to 1.69 m/sec, $p < 0.05$, respectively). There were no statistically significant differences in the noninvasive serum markers AAR (1.39 vs. 1.15, $p = 0.05$), APRI (1.14 vs. 1.31, $p = 0.52$), FIB-4 (3.50 vs. 3.65, $p = 0.77$), and the Lok index (0.63 vs. 0.41, $p = 0.30$) in the overall patient group.

In conclusion, sorafenib has potential antifibrotic effects and efficacy in patients with advanced HCC.

0058

Does Transarterial Chemoembolization Prior to Surgical Resection Improve Clinical Outcomes in Resectable Hepatocellular Carcinoma?*Young Woon Kim¹, Jung Hyun Kwon¹, Soon Woo Nam¹, Jeong Won Jang², Hye Ji Kim¹*

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

Methods: A total of 117 consecutive HCC patients who received hepatectomy at the Incheon St. Mary's Hospital between 2008 and 2015 were enrolled. 19 patients who either received more than 3 sessions of TACEs prior to resection were excluded. 98 patients underwent resection after conventional staging work up (non-TACE group) and 19 patients received a single or two sessions of TACEs before resection (TACE group).

Result: The median follow up period was 30.9 months (range, 6.5–52.9). According to the modified UICC stage, 28 (23.9%) patients were diagnosed as stage 1, 73 (62.4%) as stage 2, and 16 (13.7%) patients as stage 3. No difference was observed in terms of the age, Child-Pugh score, level of alpha-fetoprotein, and tumor stage between the two groups. In the TACE group, three new HCC lesions which were not identifiable with MRI were found in 3 patients on angiography and resected with the original lesion together. No difference was observed in the disease-free survival (DFS) and overall survival (OS) between the two groups with the mean DFS of 56.1 vs. 53.4 months ($p = 0.278$) and mean OS of 73.9 vs. 60.2 months ($p = 0.358$) in the TACE group and the non TACE group, respectively. However when the tumor size exceeded 5 cm, longer DFS was achieved in the TACE group compared to the non TACE group ($p = 0.044$).

Conclusion: TACE performed prior to surgical resection does not enhance DFS or OS in the patients with resectable HCC. However, preoperative TACE may be useful in patients with HCC exceeding 5 cm and may aid in the discovery of new lesions that were not identifiable with conventional imaging studies.

0074

The Determinants of the Survival in Sorafenib Early Non-Responders*Yuan-Hung Kuo, Jing-Houng Wang, Chao-Hung Hung, Chien-Hung Chen, Tsung-Hui Hung, Sheng-Nan Lu*

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Background/Aims: Although sorafenib is the approved treatment option in the patients with hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer (BCLC) stage C, few patients could have a good prognosis. This study aimed to evaluate the outcome of sorafenib monotherapy early non-responders.

Methods: The reimbursement criteria of Taiwan National Health Insurance (NHI) were BCLC stage C HCC with macroscopic vascular invasion (VI) or extrahepatic metastasis (Mets) and Child–Pugh (CP) class A. Radiologic assessment was performed at a 2-month interval using modified Response Evaluation Criteria in Solid Tumors. Patients with tumor progression or liver function deterioration (LD) with irreversible CP score increase ≥ 2 were disallowed to use sorafenib continually under NHI reimbursement. From Aug 2012 to Jun 2015, 415 consecutive advanced HCC patients received sorafenib under NHI in our hospital. The exclusion criteria were sorafenib with concurrent locoregional therapy, sorafenib monotherapy use more than 2 apply course under NHI and LD at sorafenib termination. Among them, 165 (39.8%) patients who had sorafenib monotherapy use ≤ 2 apply courses under NHI and CP score increase < 2 were retrospectively analyzed.

Results: Among the enrolled 165 patients, there were 51 (30.9%) Mets, 74 (44.8%) VI and 40 (24.2%) both. The median period of sorafenib use was 2.2 months. After sorafenib termination, 76 (46.1%) patients received the sequential treatments with a median survival of post sorafenib use as 10.4 months; whereas the other 89 (53.9%) received the best supportive care only with 2.33 months, $p < 0.001$. The sequential treatments included systemic chemotherapy in 13 patients with a median period of post sorafenib use as 14.5 months, radiofrequency ablation ($n = 6$; 12.2 months), transcatheter arterial embolization ($n = 6$; 8.63 months), intrahepatic arterial chemotherapy ($n = 7$; 7.97 months), second-line trial agents ($n = 12$; 7.7 months), thalidomide ($n = 17$; 6.93 months) and radiotherapy ($n = 11$; 4.97 months). During the follow-up, 119 (72.1%) patients died. The multivariate analysis associated with the better survival post sorafenib use were initial alpha-fetoprotein < 200 ng/ml (Hazard ratio (H.R): 1.77; 95% confidence interval (CI): 1.09–52.877, $p = 0.021$) and with sequential treatments (HR: 4.93; 95% CI: 2.74–8.87, $P < 0.001$). In multivariate logistic regression analysis, the independent factors contributed to post-sorafenib sequential treatment were CP score increase < 2 (Odds ratio (OR): 2.47; 95% CI: 1.09–5.6, $P = 0.03$) and Mets without VI (OR: 3.79; 95% CI: 1.14–12.56, $p = 0.029$).

Conclusions: Among sorafenib early non responders, those patients who were Mets and in good liver function reserve might afford sequential treatments and obtain a better survival.

0078

Albumin-Bilirubin Grade and Long-Term Survival in Very Early Stage Hepatocellular Carcinoma Who Received Either Resection or Ablation

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Background: The Albumin-Bilirubin (ALBI) grade was suggested as a simple, more objective evidence of assessing liver function in hepatocellular carcinoma (HCC). We tested whether ALBI can help stratify long-term outcome after resection or ablation in very early stage HCC.

Methods: A total of 536 HCC patients with the Barcelona Clinic Liver Cancer (BCLC) stage 0 (age = 57.4 ± 10.1 ; male = 77.6%; hepatitis B virus (HBV) = 80.4%), who received either resection or radiofrequency ablation (RFA) between Jan. 2007 and Dec. 2012 at Samsung Medical Center were analyzed. Ideal candidate for resection was defined by normal serum bilirubin and no clinically significant portal hypertension according to BCLC criteria.

Results: ALBI grade, underlying liver disease (HBV or others) and treatment modality (resection vs. RFA) were independent factors associated with survival. Those with ALBI grade 1 showed better 5-year survival rate than grade 2 for patients who received resection (96.8% vs. 92.5%, $p = 0.021$), as well as patients who received RFA (88.5% vs. 74.9%, $p < 0.001$), patients with HBV (91.6% vs. 86.5%, $p = 0.027$), and patients with other liver disease (88.5% vs. 62.5%, $p < 0.001$). Resection was associated with better survival than RFA (97.4% vs. 88.8% at 5-year, $p = 0.012$) among ideal candidate for resection ($n = 252$). Yet, resection was also associated with better survival than RFA in non-ideal candidate for resection ($n = 284$) (93.6% vs. 79.5% at 5-years, $p = 0.004$), with ALBI grade 1 (96.8% vs. 88.5% at 5-years, $p = 0.007$), as well as in ALBI grade 2 (92.5% vs. 74.9% at 5-years, $p = 0.004$).

Conclusion: The ALBI grade was useful for further estimating long-term survival of very early stage HCC who received resection or RFA. However, neither ALBI grade nor BCLC criteria for resection was useful to identify subgroup where less invasive RFA can show similar survival to resection in very early stage HCC.

0086

Prediction of Hepatocellular Carcinoma Recurrence after Radiofrequency Ablation Using Transient Elastography

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Objectives: The purpose of present study is to predict recurrence of hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) using Liver stiffness (LS) assessed using transient elastography (TE).

Method: A total of 228 HCC patients from multicenter between 2008 and 2015 who received LS measurement and RFA as the first-line treatment for HCC were enrolled retrospectively. Independent predictors of HCC recurrence were analyzed and the prediction accuracy of LS value were compared with other prediction models.

Results: Recurrence was developed in 125 out of 228 patients at a median of 29.3 months after RFA. Clinically diagnosed cirrhosis, platelet count, tumor number and LS value were identified as the independent predictors. When, divided into the early and late recurrence groups, liver cirrhosis, serum albumin, platelet count, spleen diameter, total tumor size, tumor number and LS value were statistically significant based on univariate analysis in the late recurrence group. LS value was identified as independent predictors in multivariate analysis, along with liver cirrhosis and spleen diameter. The accuracy of LS value alone was not inferior compared with other prediction models. (AUROC value of LS value, LSPS, LSNPS, APRI, and ASPRI = 0.805, 0.796, 0.809, 0.681 and 0.721). When the patients were divided into two groups using the optimal cutoff value (13 kPa), patients with LS values ≥ 13 kPa had a higher risk for late recurrence compared with those with LS values < 13 kPa. (HR = 4.746, $P < 0.001$; 95% CI, 2.867–7.859). The annual recurrence rate in patients with LSM values ≥ 13 kPa were also higher compared with patients with LS values < 13 kPa, which showed 62.2% in 3 years, 86.5% in 5 years and 91.0% in 7 years in ≥ 13 kPa group, whereas 17.2% in 3 years, 33.0% in 5 years and 33.0% in 7 years in < 13 kPa group ($P < 0.001$, log rank test) The cutoff value to predict high risk patients with high positive predictive value was 31.2 kPa in our study.

Conclusions: HCC recurrence after RFA have a substantial influence on long term prognosis. This work suggests that LSM can be a useful predictor of recurrence after radiofrequency ablation of HCC. Further studies are needed to validate this result.

0088

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

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Objectives: Advanced hepatocellular carcinoma (HCC) with jaundice has an extremely poor prognosis. In case of obstructive jaundice, biliary drainage can resolve jaundice, but the problem is that obstruction is not evident in many cases. We evaluated the role of endoscopic biliary drainage in patients with advanced HCC with jaundice.

Methods: From 2010 to 2015, total 70 received endoscopic biliary drainage for jaundice due to advanced HCC. Jaundice resolution was defined as follows; complete resolution: total bilirubin less than 2 mg/dl, partial resolution: total bilirubin decreased but >2 mg/dl.

Results: Child-Pugh class was B in 65.7% (46/70), C in 31.4% (22/70). BCLC stage was B in 14.2% (10/70) and C in 85.8% (60/70). Intrahepatic bile duct dilatation was observed in 50% (35/70) and tumor location were whole liver in 27.1% (19/70) and whole right lobe in 27.1% (19/70). Table 1 showed baseline characteristics of 70 patients. Success rate of biliary drainage was 95% (67/70). After drainage, jaundice was resolved completely in 27.1% (19/70), partially in 28.5% (20/70). The median time to resolution was 19 days (range, 2–96 days). However, in these patients, jaundice was aggravated in 74.3% (29/39) median 88 days (range, 5–399 days) after resolution. The presence of intrahepatic bile duct dilatation was significantly associated with complete resolution of jaundice in multivariate analysis ($p = 0.040$). In overall, 90 days survival rate was 24.2% and median survival was 30 days (95% CI; 9–50 days). Predicting factors for overall survival was jaundice resolution ($p < 0.001$), Child-Pugh class ($p = 0.019$), aspartate aminotransferase ($p = 0.021$) and BCLC stage ($p = 0.036$) in multivariate analysis, respectively.

Conclusions: Through endoscopic biliary drainage, jaundice was improved in 55.7% with advanced HCC and survival can be prolonged in patients who showed jaundice resolution. In jaundice in presence of intrahepatic bile duct dilatation, biliary drainage can be appropriate palliative treatment in advanced HCC patients.

0089

Three-Dimensional Conformal Radiotherapy for Portal Vein Tumor Thrombosis in Advanced Hepatocellular Carcinoma*Jeong Heo, Hyun Young Woo, Moon Won Lee, Won Lim, Won Tak Kim, Ki Tae Yoon, Young Mi Hong, Mong Cho*

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Objectives: We sought to evaluate the clinical outcomes of 3-dimensional conformal radiation therapy (3D-CRT) for portal vein tumor thrombosis (PVTT) in patients with advanced hepatocellular carcinoma.

Methods: We retrospectively analyzed data on 99 patients who received 3D-CRT for PVTT alone between June 2002 and December 2015. Response was evaluated following the Response Evaluation Criteria in Solid Tumors.

Results: Twenty one patients (21.2%) had age over 65 years and forty patients (40.4%) had Child-Pugh class B. The Eastern Cooperative Oncology Group performance status was 2 in 23 patients (23.2%). Forty eight patients (48.5%) had main or bilateral PVTT. The median irradiation dose was 50 Gy (range, 10–60 Gy), the daily median dose was 2.172 Gy (range, 1.8–3 Gy) and median number of fraction was 25 (2–30). 70 (70.7%) patients treated with transarterial chemoembolization (TACE) followed by 3D-CRT and 29 patients were treated with 3D-CRT alone. PVTT response was complete response in 3 patients (3.1%), partial response in 36 (36.4%), stable disease in 35 (35.4%), and progressive disease in 17 (17.2%). In overall tumor response, complete response was 1 (1.0%), partial response was 22 (22.2%), stable disease was 23 (23.2%), and progressive disease was 46 (46.5%). PVTT response was significantly associated with number of radiation fraction ($p = 0.044$). Overall objective tumor response was significantly associated with number of radiation fraction ($p = 0.040$) and metastatic status ($p = 0.046$). There were 5 cases of grade 3 liver function aggravation during or 1 months after radiotherapy. The 1-year and 2-year survival rate was 40.2% and 19.3%, respectively. Survival was significantly associated with overall tumor response ($p = 0.034$), etiology ($p = 0.007$) and number of radiation fraction ($p = 0.035$).

Conclusion: Conformal radiotherapy with or without for PVTT could be chosen as a palliative treatment modality in patients with unfavorable conditions (liver, patient, or tumor factors).

0091

The Optimal Surveillance Tools to Detect Postoperative HCC Recurrence: The Diagnostic Accuracy of Tumor Markers in a Single Center Cohort*Sung Hyun Kim, Gi Hong Choi*

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Background: Recurrence after surgical resection is up to 70~80% at 5 years. However, until now optimal surveillance guideline for postsurgical recurrence of hepatocellular carcinoma (HCC) has not been established. In this study, we analyzed the accuracy of the surveillance tool.

Methods: From January 2006 to December 2010, 131 patients who were confirmed recurrent HCC after curative resection, were retrospectively reviewed. We used liver dynamic three-phasic CT with tumor markers (AFP and PIVKA II) every three months as surveillance for surgically resected HCC patients. Dividing three groups into AFP, PIVKA II and AFP+PIVKA II group, we evaluated the effect of early recurrence HCC. We defined the early recurrence as less than 3 cm and three recurrent tumors.

Results: On McNemar test, there was no significant difference between accuracy rates of each tumor marker. (p value: 0.699) On ROC curve, only AFP+PIVKA II group showed statistical significant to detect the early recurrence HCC. (AFP; AUC: 0.618, p value: 0.059, PIVKA II; AUC: 0.618 p value: 0.060 and AFP+PIVKA II; AUC: 0.684, p value: 0.003).

Conclusion: Combined AFP and PIVKA II could be a reasonable surveillance tools for detection of early recurrent HCC after surgical resection.

0094

ALBI Grade Is a Good Grading System for Liver Function in Patients with Hepatocellular Carcinoma*Young Kul Jung¹, Sang Jun Suh¹, Hyung Joon Yim¹, Ji Hoon Kim², Jong Eun Yeon², Kwan Soo Byun², Yeon Seok Seon³, Soon Ho Um³*¹Korea University Ansan Hospital, Ansan, ²Korea University Guro Hospital, Seoul, ³Korea University Anam Hospital, Seoul, Republic of Korea

Background and Aims: The Albumin-Bilirubin (ALBI) grade has been proposed as a simple, objective method of assessing liver function. The prognostic performance of the ALBI grade in the patients with hepatocellular carcinoma (HCC) was investigated in this study.

Methods: Total 2,099 patients with HCC of the three tertiary hospitals in Korea were analyzed retrospectively. The discriminative performance in survival analysis of the ALBI

grade was compared with the Child-Pugh (C-P) grade in different stages or treatments.

Results: The median follow up duration was 16.2 months (Range: 0–138.5). The median survival times were 49.7 months in C-P grade A (65.8%), 12.4 months in C-P grade B (25.5%), 4.2 months in C-P grade C (8.6%) (p < 0.001, Harrell's C 0.68, Somers' D 0.36). The median survival times were 84.2 months in ALBI grade 1 (32.8%), 25.5 months in ALBI grade 2 (53.5%), 7.7 months in ALBI grade 3 (13.7%) (p < 0.001, Harrell's C 0.682, Somers' D 0.364). In early UICC stages, the ALBI grade showed better discriminative performance than the C-P grade (Harrell's C: 0.676 (C-P grade) vs. 0.703 (ALBI grade), Somers' D: 0.353 (C-P grade) vs. 0.406 (ALBI grade)). In curative treatments, the ALBI grade showed better discriminative performance than the C-P grade (Harrell's C: 0.624 (C-P grade) vs. 0.667 (ALBI grade), Somers' D: 0.248 (C-P grade) vs. 0.334 (ALBI grade)).

Conclusions: The ALBI grade showed comparable discriminative performance in survival analysis and better distribution of the grades in HCC. It could be a good alternative grading system for liver function in patients with HCC.

0097

Comparing Treatment Outcomes between Radioembolization Using Yttrium-90 Microspheres and Concurrent Chemoradiation Therapy for Locally Advanced for Hepatocellular Carcinoma*Jeong Eun Song¹, Kyu Sik Jung¹, Do Young Kim^{1,4}, Jinsil Seong^{2,4}, Jong Yun Won^{3,4}, Beom Kyung Kim¹, Seung Up Kim^{1,4}, Jun Yong Park^{1,4}, Sang Hoon Ahn^{1,4}, Kwang-Hyub Han^{1,4}*¹Department of Internal Medicine, Yonsei University College of Medicine, Seoul, ²Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, ³Department of Radiology, Yonsei University College of Medicine, Seoul, ⁴Liver Cancer Special Clinic, Yonsei University College of Medicine, Seoul, Republic of Korea

Objectives: Previous studies revealed that both of radioembolization with yttrium-90 (⁹⁰Y) and concurrent chemoradiation therapy (CCRT) showed comparably good treatment outcome in the intermediate and advanced stages of HCC. The aim of this study is to comparing treatment outcome between radioembolization and CCRT in the intermediate and advanced stages of HCC.

Methods: In this retrospective study, 209 treatment-naive patients with BCLC stage B (n = 28) or C (n = 181), who were treated by CCRT (n = 144) or radioembolization with ⁹⁰Y (n = 65), were analyzed. Propensity score (PS) was calculated and matched in a 1:1 ratio for CCRT vs. radioembolization using age, tumor size, tumor number, portal vein thrombosis,

BCLC staging. Overall survival (OS), progression free survival (PFS), tumor response at 1 month after treatment, and complication rate were compared between CCRT group and radioembolization group.

Results: Among 209 patients, 124 (62 on CCRT, 62 on radioembolization) were selected by PS matching. OS (13.2 months for CCRT group vs. 14.0 months for radioembolization group, $P = 0.435$) and PFS (7.8 months for CCRT vs. 6.9 months for radioembolization group, $P = 0.437$) was comparable between two groups. In tumor response at 1 month after treatment, objective response rate (complete response or partial response) was significantly higher in CCRT group than radioembolization group (46.8% vs. 16.1%, $P < 0.001$), but disease control rate (complete response, partial response or, stable disease) was higher in radioembolization group than CCRT group (77.4% vs. 90.3%, $P = 0.051$). Complication related treatment was lower in radioembolization group with marginal statistical significance (17.7% vs. 4.8%, $P = 0.022$), but the proportion of patients, who underwent curative treatment (surgery or liver transplantation) according to down-staging of HCC, tend to be higher in CCRT group (24.2% vs. 8.1%, $P = 0.015$).

Conclusions: Both CCRT and radioembolization revealed comparable response rate and survival in the intermediate and advanced stages. Despite similar OS and PFS, it is important to select proper candidate for each treatment modality considering patients tumor burden and liver functions.

0100

Sarcopenia as a Predictor of Survival and an Objective Measure of Performance Status in Hepatocellular Carcinoma

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Objectives: The prognostic impact of sarcopenia has not been clearly demonstrated in patients newly diagnosed with hepatocellular carcinoma (HCC), especially those without symptoms.

Method: Area of skeletal muscle and abdominal fat were measured at L3 level of computed tomography scan in 132 patients newly diagnosed with HCC between Jan 2007 to Jun 2011. Sarcopenia was defined as L3 skeletal muscle index of ≤ 52.4 cm²/m² for male and ≤ 38.5 cm²/m² for female. Baseline data were analyzed to determine the effect of sarcopenia on overall survival (OS) using the univariate and Cox multivariate analyses in overall and propensity-score matched cohorts. The impact of sarcopenia in asymptomatic vs. symptomatic patients was evaluated.

Results: Sarcopenic patients (32 out of 132) were older (65.3 vs. 57.0 years old) and had lower body mass index (21.0 vs. 24.0 kg/m²), total fat (55.7 vs. 68.0 cm²/m²), and subcutaneous fat (21.9 vs. 29.2 cm²/m²) area. The presence of sarcopenia dichotomized patients with regard to OS (median 41.2 vs. 13.8 months, $P = 0.001$). Multivariate analysis found that sarcopenia (hazard ratio [HR], 2.15, $P = 0.008$), alpha-feto-protein (HR, 2.79, $P = 0.004$), Child-Pugh stage (HR, 2.38, $P = 0.017$), infiltrative tumor (HR, 2.29, $P = 0.021$), and BCLC stage ($P < 0.001$) were predictive of OS. In a propensity score-matched cohort, sarcopenia (HR, 5.50, $P = 0.027$) was the only predictive factor. In particular, asymptomatic patients with sarcopenia had a poor OS than patients without sarcopenia (median 69.6 vs. 22.2 months, $P < 0.001$), while no significant impact in symptomatic patients (median 17.2 vs. 9.7 months, $P = 0.26$). Subdividing asymptomatic patients of BCLC A and B stages according to sarcopenia status improved the predictive ability of staging system (c-index, 0.87 vs. 0.67, $P < 0.001$).

Conclusions: Sarcopenia is an independent prognostic factor in patients newly diagnosed with HCC, especially those without symptoms. Subdividing BCLC A and B stages according to sarcopenia status showed a better stratification.

Radiology

0010

Use of Gadobenate Dimeglumine (Multi-Hance) Dynamic MRI for Early Detection of HCC in Atypical Small Hepatic Focal Lesions

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Background: Multi-hance is a novel contrast medium which can be used not only as a non specific extracellular contrast agent for dynamic imaging of the liver, but also as a liver specific agent for the acquisition of hepatobiliary-phase images which is more helpful in evaluation of small atypical hepatic focal lesions (≤ 3 cm).

Aim: Evaluation of multi-hance dynamic MRI as a new modality in early detection of HCC.

Material and Methods: Twenty cirrhotic patients with a small hepatic focal lesion (less than 3 cm in diameter), detected by imaging (U/S and tri-phasic CT were subject to dynamic MRI with multi-hance contrast. All patients had a liver biopsy stained with HSP-70, Glypican-3, and glutamine synthetase to confirm the diagnosis of HCC.

Results: Five out of 20 patients (25%) with atypical focal lesions, proved to have HCC by histology, however, only 4 out of 5 histologically proved HCC patients (80%), were shown to have typical criteria on multi-hance imaging.

Conclusion: Multi-hance dynamic MRI is a promising new diagnostic modality for early detection of HCC, however, future studies on larger numbers of patients are warranted to precisely detect the sensitivity, specificity, positive and negative predicative values of this new modality.

0015

MR Imaging of Combined Hepatocellular-Cholangiocarcinoma in Normal, Fibrotic, and Cirrhotic Livers: A Comparative Study

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Objectives: To compare MR imaging features of combined hepatocellular-cholangiocarcinoma (cHCC-CC) in normal, fibrotic and cirrhotic liver.

Methods: A total of 64 patients with 67 pathologically proven cHCC-CC were retrospectively analyzed. Patients were classified into three groups according to the patients' liver condition: patients with normal liver (F0, group 1), fibrosis without cirrhosis (F1-3, group 2), and cirrhosis (F4, group 3). The morphological and MR signal features on T1, T2-weighted, dynamic-enhanced, diffusion-weighted imaging, as well as the accompanying imaging findings were evaluated and compared.

Results: There were 12, 19, and 33 patients in group 1, 2 and 3, respectively. Tumors in the fibrotic and cirrhotic liver were smaller than those in the normal liver, and tumors with cirrhosis had the smallest size ($P = 0.0326$). No statistical difference was found when comparing the signal intensity on T2-weighted imaging ($P = 0.496$), but iso- or hypointense lesions were only found in the fibrosis ($n = 2$) or cirrhosis group ($n = 2$). Enhancement pattern was different between groups, the washout pattern was more often seen in the cirrhosis group ($P = 0.049$); and the accompanying septate enhancement was also more commonly seen in the cirrhosis group ($P = 0.048$). The ADC values of the lesions were not different among the three groups ($P = 0.899$).

Conclusions: MRI may provide valuable information for the diagnosis and differential diagnosis of cHCC-CC in normal,

fibrotic and cirrhotic liver. The nodule size, enhancement patterns and the presence of septate enhancement are potential predictors for differentiation.

0016

The Rat Hepatic Stellate Cell was Activated by PI3K/Akt Signaling Pathway after Radiotherapy in vitro

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Objective: To investigate the phosphatidyl inositol 3 kinase-protein kinase B (PI3K/Akt) signaling pathway in the hepatic stellate cells (HSC) by X-ray irradiation, explore the relationship of the PI3K/Akt signaling pathway and the activation of HSC.

Methods: HSC-T6 were exposed to the different doses of 6 MV X-ray (0 Gy, 10 Gy, 20 Gy) irradiation and PI3K/Akt signaling pathway inhibitor LY294002. The apoptosis rate was detected by Flow Cytometry (FCM). The expression of transforming growth factor $\beta 1$ (TGF- $\beta 1$) was detected by ELISA assay. The expression of Akt and α -smooth muscle actin (α -SMA) mRNA were detected by real-time PCR. The expression of p-Akt was detected by Western blot assay.

Results: Compared with the control group, the apoptosis rate of the 10 and 20 Gy group increased with the increase of irradiation dose ($t = 8.43, 11.63, P < 0.05$) by FCM; The apoptosis rate decreased after the same irradiation dose plus inhibitor group ($t = 8.09, 4.89, P < 0.05$). Compared with the control group, the expression of TGF- $\beta 1$ increased with the increase of irradiation dose in the 10 and 20 Gy group ($t = 11.51, 19.02, P < 0.05$) by ELISA assay; Compared with the simple irradiation group, the expression of TGF- $\beta 1$ decreased after the same irradiation dose plus inhibitor group ($t = 6.17, 10.04, P < 0.05$). RT-PCR assay showed that, compared with the 10 Gy group, the expression of Akt and α -SMA mRNA increased in the 20 Gy group ($t = 4.89, 7.80, P < 0.05$), it decreased in the 10 Gy+LY294002 group ($t = 13.66, 15.11, P < 0.05$); Compared with the 20 Gy group, the expression of Akt and α -SMA mRNA decreased in the 20 Gy+LY294002 group ($t = 6.20, 6.85, P < 0.05$). Western blot assay showed that, compared with the control group, the expression of p-Akt increased with the increase of irradiation dose in the 10 and 20 Gy group ($t = 5.74, 31.23, P < 0.05$); Compared with the simple irradiation group, the expression of p-Akt decreased after the same irradiation dose plus inhibitor group ($t = 10.34, 23.84, P < 0.05$).

Conclusions: X-ray irradiation active hepatic stellate cell, which may be related with PI3K/Akt signaling pathways activation. PI3K/Akt signaling pathway may become a potential therapeutic target for radiation-induced liver injury.

0041

Washout Appearance in Gd-EOB-DTPA-Enhanced MR Imaging: Differentiating Feature between Hepatocellular Carcinoma (HCC) with Paradoxical Uptake on the Hepatobiliary Phase (HBP) and Focal Nodular Hyperplasia (FNH)-Like Nodule*Chang-Hee Lee, Jeong Woo Kim, Cheol Min Park, Kyeong Ah Kim*

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Objectives: To identify the most reliable imaging features for differentiating hepatocellular carcinoma with paradoxical uptake on the hepatobiliary phase (HCC_{pdx}) from focal nodular hyperplasia (FNH)-like nodule in Gd-EOB-DTPA-enhanced magnetic resonance imaging (MRI).

Methods: Twenty patients with HCCs_{pdx} and 21 patients with FNH-like nodules were included. The following MRI features were evaluated: signal intensity (SI) on T1-, T2-, and diffusion-weighted imaging (DWI), arterial enhancement pattern, washout appearance on the portal venous phase (PVP) and/or transitional phase (TP), uptake pattern on the hepatobiliary phase (HBP), 'T2 scar', 'EOB scar', and chemical shift on in- and out-of-phase images. Multivariate logistic regression analysis was performed to assess MRI features for prediction of HCCs_{pdx}.

Results: Compared with FNH-like nodules, HCCs_{pdx} had significantly more frequent heterogeneous T1 SI, T2 hyperintensity, heterogeneous arterial enhancement, washout appearance on the PVP and/or TP, heterogeneous uptake on the HBP, absence of 'EOB scar', and hyperintensity on DWI. Multivariate logistic regression analysis revealed washout appearance as the only independent imaging feature associated with HCCs_{pdx} (odds ratio, 7.019; $p = 0.042$). Washout appearance also showed the best diagnostic performance.

Conclusion: Washout appearance on the PVP and/or TP is the most reliable imaging feature for differentiating HCCs_{pdx} from FNH-like nodules.

0061

Post-Operative Biloma as a Risk Factor for Late Recurrence of Hepatocellular Carcinoma in BCLC Stage B Patients*Yu-Chien Chang¹, Chih-Horng Wu¹, Ming-Chih Ho², Yu-Yun Shao³, Po-Chin Liang¹, Tiffany Ting-Fang Shih¹, Yeun-Chung Chang¹*

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Objective: The aim of this retrospective study was to evaluate whether biloma in postoperative images correlated with hepatocellular carcinoma (HCC) recurrence after surgical resection.

Methods: Seventy-two patients with solitary or multiple HCC lesions treated by hepatectomy were evaluated. They were categorized according to The Barcelona clinic liver cancer (BCLC) staging classification. 1–2 months postoperative CT or MR was evaluated for post-operative condition and recorded for presence of biloma or not. After 2 years follow up, HCC recurrence was divided into early (less than half year) and late (between half and 2 years) recurrence and correlate with imaging findings.

Results: Of 72 patients, 43, 24 and 5 cases were in BCLC stage A, B and C, respectively. Among the BCLC stage B group, 11 persons had biloma in the postoperative CT or MR and 7 cases had late recurrence and 2 cases had no recurrence. In the non-biloma group of 13 cases, 7 persons had no recurrence and 2 persons had late recurrence with statistically significant ($p < 0.05$).

Conclusion: We proposed that the appearing of biloma in the early follow up indicated local increased inflammatory stimulation and would probably had correlation with tumor recurrence. In our study, we found the postoperative biloma correlated with late recurrence of HCC in BCLC stage B patients.

0071

Intraoperative Radiofrequency Ablation for Hepatic Tumors: The Effect of Pringle's Maneuver on Ablation Volume*Yang Shin Park*

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Purpose: To evaluate intraoperative radiofrequency ablation (RFA) with or without Pringle's maneuver for small hepatic tumors in comparison with percutaneous RFA.

Materials and Methods: We retrospectively assessed 69 patients (59 men, 10 women) who underwent ultrasonog-

raphy-guided RFA for treatment of small hepatic tumors from January 2013 to December 2015. 23 patients underwent intraoperative RFA and 46 patients underwent percutaneous RFA. All ablations were applied in a single session using 3-cm active-tip electrodes. All patients underwent scheduled CT 1 month after RFA. Using CT scan of portal venous phase, the RFA volume was measured with manual segmentation. Patients' characteristics, procedure type (intraoperative or percutaneous), Pringle maneuver, total ablation time, electrode size, tumor location (subcapsular or central location), tumor size, and underlying liver disease were assessed. Univariate and multivariate analyses were performed to evaluate which variables were most influential on RFA volumes. Two-way ANOVA compared RFA volumes between procedure types with or without Pringle's maneuver and between different size of electrodes.

Results: In univariate and multivariate analyses, procedure type, Pringle maneuver, and electrode size were significant factors in terms of RFA volume ($P < 0.05$). In comparison to percutaneous RFA, intraoperative RFA with Pringle's maneuver using 15 G electrode showed 5.6 times larger RFA volume (mean, $18.6 \pm 4.2 \text{ cm}^3$ vs. $105.8 \pm 10.3 \text{ cm}^3$).

Conclusions: Intraoperative RFA with Pringle's maneuver demonstrated the largest ablated volume. Therefore, intraoperative RFA with Pringle maneuver can be applied to obtain larger ablated volume and adequate safety margin especially in larger tumors, centrally located tumors, or perivascular tumors.

0093

Easy Detection of Tumor-Feeding Branches of Hepatocellular Carcinoma with SYNAPSE VINCENT during Transcatheter Arterial Chemoembolization

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Purpose: To evaluate the usefulness of transcatheter arterial chemoembolization (TACE) guidance software that uses the volume analyzer SYNAPSE VINCENT in detecting tumor-feeding branches and expecting embolization area of hepatocellular carcinoma (HCC).

Material and Methods: The application soft of SYNAPSE VINCENT, liver analysis, were used in chemoembolization of 6 patients of 7 HCCs. Detectability of tumor-feeding branches was compared versus that of nonselective digital subtraction angiography (DSA). Embolization area of chemoembolization was evaluated by within one week CT findings after TACE.

Result: The maximal diameter of these tumors ranges 10 to 42 mm (mean \pm SD, 20.9 ± 10.6 mm). The average time for detect tumor-feeding branches was 242 seconds. Total time to detect tumor-feeding branches and simulate the embolization area was 384 seconds. All cases could detect all tumor-feeding branches of HCC and expected embolization area of simulation of SYNAPSE VINCENT were almost nearly CT after TACE.

Conclusion: This new technology has possibilities to reduce the amount of radiation exposure and to improve the therapeutic effect of TACE.

Surgery, Transplantation

0008

Less Cost by Using Hanging Maneuver and Pringle Maneuver in Left Lateral Hepatectomy through Small Laparotomy Wound for Hepatocellular Carcinoma

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Background and Objectives: Laparoscopic segmentectomy for hepatocellular carcinoma (HCC) located in the left lateral segment (LLS) is thought to be a standard protocol with several advantages, such as small wound, few blood loss, and short hospital stay. However, there are still many disadvantages during perform laparoscopic LLS segmentectomy. We will present the technique to perform LLS segmentectomy with small incision, hanging maneuver and Pringle maneuver in patients HCC at LLS of the liver.

Methods: Between November 2010 and Apr 2015, hepatectomies through small incision for 8 patients with HCC were performed at Kaohsiung Chang Gung Memorial Hospital, Taiwan. Perioperative and postoperative results, such as operation time, blood loss, incisional width, and postoperative stay were recorded and analysed.

Results: Results demonstrated that modified LLS segmentectomy by the author's team was performed successfully in patient with HCC with fewer blood loss, smaller incisional width, and lower hospital cost than traditional open surgery. In addition, the instrument cost and blood loss in our series were less than that in laparoscopic LLS segmentectomy in published literature.

Conclusions: Authors concluded that minimally incisional segmentectomy, with less cost and technical demanding, could be an alternative choice in patient with HCC at LLS.

0018

Long Term Survival to Hepatocellular Carcinoma through Utilization of Multifocal Extrahepatic Metastases and Surgical Treatments*Joji Yamamoto*

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Objectives: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Extrahepatic metastasis is relatively rare and the prognosis is extremely poor.

Method and Results: Herein we describe a case of a 59 year-old male who has undertaken right tri-segmentectomy for giant HCC with portal vein thrombus 6 years ago. 1 year after the initial operation, the patient showed right adrenal gland metastasis with tumor thrombus in inferior vena cava and 3 year after the second operation, he showed a single lung metastasis. Both metastases were treated through surgical procedures. Our case suggests that a certain patient with progressive HCC with multiple distant metastases may archive long term survival through surgical procedures. Hepatocellular carcinoma, typically occurs in the hepatitis or cirrhosis of the liver, and is often associated with hepatitis C or hepatitis B viral infection. Extrahepatic metastasis of HCC is relatively rare. However, as treatment for HCC is currently being developed through methods like surgery, transarterial chemo-embolization, and radiofrequency ablation, the detection of extrahepatic metastasis is becoming more sensitive and more accurate in regard to development of imaging modalities. The numbers of HCC metastasis is increasing clinically. The most frequent sites of HCC metastasis are lung, abdominal lymphnodes, bone and adrenal gland. The prognosis of patients with HCC metastasis is extremely poor and long-term survival is often not expected. Uchino et al have reported that the median survival after diagnosis of extrahepatic metastasis was only 8.1 months. The treatment for extrahepatic metastasis of HCC is controversial. Sorafenib, molecularly targeted agents, is the only effective systemic therapy for the treatment of HCC at the moment. However, the results of the treatment are still unsatisfactory.

Conclusions: We reported a rare case of HCC metastases to adrenal gland with IVC tumor thrombus and lung, surviving more than 6 years after the initial operation. We herein report a case involving the adrenal gland and lung metastasis which were treated with surgical procedures. The clinical evaluation of the patient has been satisfactory for 6 years after liver resection, 5 years after adrenalectomy with tumor thrombus removal and 2 year after lung resection, providing the satisfactory result of no recurrence of HCC in the remnant liver or other organs. Therefore, surgical approach toward metastases of HCC should be considered and provides the best chance for be long-term disease free survival.

0042

Management of Pregnancy-Associated Hepatocellular Carcinoma: A Case Series*Kevin Ka Wan Chu, Albert C.Y. Chan, Tan-To Cheung, Siu-Ho Chok, Chung-Mau Lo, Ronnie Poon*

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Introduction: Pregnancy-associated hepatocellular carcinoma is an uncommon phenomenon and is seldom reported. Our aim was to evaluate the natural history and treatment outcome of this rare disease entity.

Methods: Between January 1992 and June 2015, five cases of HCC associated with pregnancy were referred to our centre. The management of their disease was according to treatment protocol during the time periods. Their demographics, obstetric outcome, clinico-pathological course and survival were reviewed.

Results: All of the ladies were diagnosed at young age (25–36 year-old). Three of them were diagnosed at their first pregnancy while two of them were diagnosed at their second pregnancy. The gestational ages at diagnosis were all late in their gestation, varied from 28 weeks to 2 weeks post-partum. All of them enjoyed good health except hepatitis B. For the disease characteristics, all of these ladies had advanced disease. Four of the ladies had multifocal disease while another had huge solitary HCC. Size of largest tumour varied from 7 to 20 cm. The alpha-fetoprotein on diagnosis were elevated, ranging from 58 ng/ml to 60500 ng/ml. Four of them had Child A cirrhosis while the other presented with Child B cirrhosis. Hepatectomy was performed for four of these patients. In all the operative specimens, the non-tumour liver histology showed no cirrhosis. Four of these patients succumbed of the disease with survival after diagnosis varied from 26 days to 35 weeks, and one patient remained recurrence-free at 6 months after operation. Another patient was still under surveillance with disease free survival more than 6 months.

Conclusion: Pregnancy associated hepatocellular carcinoma has an aggressive tumor behavior. For women with known hepatitis B infection, screening of HCC should be advocated at the early stage of pregnancy.

0051

The Comparison of Oncologic and Clinical Outcomes of Laparoscopic and Open Liver Resection for Hepatocellular Carcinoma*Hong-Jin Kim, Dong-Shik Lee, Sung-Su Yun*

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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 (possible to change). (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.

0055

Microwave Ablation versus Liver Resection for the Treatment of Hepatocellular Carcinoma: A Propensity Score Matching Study

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Background and Objectives: Whether the liver resection or ablation should be the first-line treatment for hepatocellular carcinoma (HCC) in patients who are candidates for both remains a hot debate. Retrospective studies and meta-analysis showed that microwave ablation (MWA) is at least as effective as, if not superior than, radiofrequency ablation in treating HCC. Studies comparing MWA and liver resection are lacking. The aim of this study is to evaluate the survival of patients who were treated with liver resection and MWA and to evaluate if the newly developed Albumin-Bilirubin (ALBI)

grade can help in patient selections for liver resection or ablation.

Methods: This is a retrospective analysis on patients who received curative liver resection and MWA for primary HCC from March 2009 to December 2015. Baseline clinical and laboratory parameters were retrieved and reviewed from the hospital database. To correct the difference in clinicopathological factors between the two groups, propensity score matching was used at 1:1 ratio. The ALBI grade was evaluated for their abilities of patient selection. Overall and disease-free survivals were compared between two groups.

Results: A total of 442 patients underwent MWA and liver resection for primary HCC during the study period. Among them, 63 patients received MWA and 379 patients received liver resection. The 1-, 3-, 5-year overall survival of MWA and liver resection were 98.4%, 72.3%, 61.3% and 91.4%, 77.4%, 68.2% respectively ($p = 0.734$). Compared with the resection group, MWA resulted in a higher recurrence rate (65.1% vs. 43.3%, $p = 0.001$ and a shorter disease-free survival. The 1-, 3-, 5-year disease-free survival of MWA and liver resection were 62.5%, 30.6%, 17.5% and 70.5%, 56.2%, 43.7% respectively ($p < 0.001$.) MWA group was associated with older patients, more cirrhotic liver, and smaller tumour.

Propensity scoring matching was used and resulted in 63 matched pairs for further analysis. Liver resection still offered lower recurrence rate and superior disease-free survival to MWA. Subgroup analysis was performed on patients with ALBI grade 1 and ALBI grade 2 or 3. While liver resection still offered better overall and disease-free survivals in patients with ALBI grade 1, MWA provided a significantly better overall survival and a non-significant trend of better disease-free survival in patients with ALBI grade 2 or 3.

Conclusions: Liver resection offered superior disease-free survival to MWA in patients with primary HCC. The ALBI grade could identify patients with worse liver function who might gain survival advantage from MWA.

0076

The Epidemiology of HCC in Poland

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Background: HCC is predominant worldwide. The incidence rate and mortality is on a rise. According to WHO, Poland fits in the medium risk group for HCC.

Materials and Methods: The number of new cases and HCC-caused deaths during the recent years were determined, as well, morbidity and mortality rates in women and men, all based on the data from Cancer Center and National Health Fund. Data from Polish Transplant Coordinating Center ‘Poltransplant’ was used to determine the number of LTx and HCC etiology.

Results: The epidemiology data is not exact. According to National Health Fund the total number of new cases increases every year, reaching 1851 in 2013. Incidence rate increases as well, climbing from 3.1 in 2008 to 4.8 in 2013. The data from Cancer Center deviates from previous in terms of total number and incidence rate. The total number of HCC-caused deaths fluctuates around 2000 yearly. Mortality rate differs around 5 and is higher in men (M –5.7; W –4.7). The incidence and mortality rate increase after the age of 50. The number of LTx due to HCC steadily increases. The percentage of recipients with HCC in 2005 equaled 4.27 and rose to 21.68% in 2015. Amongst 62 recipients transplanted because of HCC, 11.2% constituted the group with cirrhosis related to Hep-C and 3.5% to Hep-B infections.

Conclusions: The incidence rate of HCC in Poland is underestimated and gradually increasing, though close to that in Western Europe. Most frequent cause of HCC is post-hepatitis C cirrhosis. The highest incidence and mortality rate regards men after 50. The number of deaths related to HCC increases; one in five patients receive LTx because of HCC.

For a 5 year period, 134 patients with liver tumors were treated. Laparoscopy technique was used in 47 patients (35.1%).

Transection of liver parenchyma can be performed by Harmonic scalpel, CUSA – Cavitron Ultrasonic Surgical Aspirator, Water Jet, Ligasure, Staplers, Bipolar coagulation, or by Radiofrequency ablation.

Combination of this methods, mainly CUSA, Bipolar coagulation and Harmonic scalpel looks to be adequate for liver resections.

Results: For a 5 Year period, 47 of 134 (35.1%) laparoscopic liver resections were included. Complications occurred in 3 patients (6.4%). Mean blood loss was 68.7 ml. Mean surgical time was 151 minutes in Laparoscopic Liver Resections.

Conclusions: Laparoscopic liver resections are safe and feasible with acceptable morbidity and mortality for both minor and major hepatic resections. The laparoscopic approach proves the benefit of a shorter hospital stay at Intensive Care Unit, lower blood loss, less analgesia, smaller incisions, a better cosmetic result, and faster recovery. Since mini invasive surgery of the liver was first introduced, laparoscopic liver surgery has been considered a promising technique due to fact that no reconstruction is demanded for resection. However, the procedure should be performed by a surgical team expert in hepatobiliary and laparoscopic surgery in properly selected patients.

0081

Laparoscopic Liver Resections: Modalities and Options

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Background: Minimally invasive hepatic resection approaches include pure laparoscopic, hand-assisted laparoscopic, and a laparoscopic-assisted open ‘hybrid’ approach. Minimally invasive operations are associated with lower perioperative morbidity with the same oncologic outcomes.

Ultrasound guidance is an important tool in the laparoscopic approach, enabling surgeons to target lesions anywhere within the liver, identify size and shape of the lesions.

Materials and Methods: From 2004 laparoscopic approach was used for biopsytization of liver tumors, Radiofrequency ablations of metastases in liver and for marsupialization of liver cyst. From 2007, with more experiences in laparoscopic liver surgery, resections of primary and secondary liver tumors were performed.

0090

Clinical Outcomes after Transarterial Embolisation and Stereotactic Body Radiotherapy as Neoadjuvant Therapy for Large Solitary Right Lobe Hepatocellular Carcinoma Greater Than 10 cm

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Objectives: Surgical resection remains the only hope of cure in patients with large right lobe hepatocellular carcinoma (HCC) >10 cm. In such patients with good liver reserve but inadequate future liver remnant volume (FLRV), we have reported earlier that transarterial chemoembolisation (TACE) combined with stereotactic body radiotherapy (SBRT) can be employed as a feasible and safe neoadjuvant therapy to downstage the tumour to facilitate subsequent hepatectomy. This study aimed to further evaluate our experience with regard to surgical outcomes as well as overall survival in these patients.

Method: From July 2009 to December 2014, 15 patients with large (≥10 cm) solitary right lobe HCC with good liver reserve (Child A) were treated by TACE combined with SBRT. The clinicopathological factors and clinical outcome measures were reviewed retrospectively.

Results: Of these 15 patients, hepatectomy was ultimately performed in 12 patients with the tumours successfully resected. Portal vein thrombosis was seen in four patients. Two patients received portal vein embolisation (PVE) prior to hepatectomy because the FLRV were still inadequate even after TACE and SBRT. Four patients had received target therapy. Two hospital mortality was reported. One patient died of acute myocardial infarction on postoperative day 7; while the other died of hospital acquired pneumonia on postoperative day 80. Overall survival was 58.3% (as at December 2015). Median survival was 31 months. Recurrence occurred in 7 patients. One patient could receive further surgical resection; another one was treated with percutaneous radiofrequency ablation, while others were mainly treated with TACE or symptomatic care.

Conclusions: TACE combined with SBRT was a feasible and safe option to downstage large solitary right lobe HCC greater than 10 cm, with or without portal vein thrombosis, with survival benefits. The role of additional PVE and/ or target therapy remained to be addressed.

0095

Fairness of Liver Graft Allocation Under Current HCC MELD Score Exception Policy in Hong Kong

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Objective: This study is to determine whether liver transplant waitlist candidates with hepatocellular carcinoma (HCC) are over-advantaged against the non-HCC candidates for graft allocation under current HCC prioritization scheme.

Background: The priority of liver graft access in Hong Kong is ranked by candidates' Model of End-stage Liver Disease (MELD) scores. MELD score was originally developed to model the survival of patients with decompensated cirrhosis, it is unable to reflect the risk of mortality in candidates listed for indications other than liver failure, such as hepatocellular carcinoma, who has relatively preserved liver function. In an attempt to fairly represent the urgency of need for liver transplant in these candidates, a prioritization scheme to assign a MELD score bonus is implemented. In Hong Kong, HCC candidates with T2 disease receive 18 MELD score points if the tumor remained in T2 after an observation period of 6 months. An increment of 2 MELD score points is given for every 3 months without disease progression. There is concern that such a scheme would over-prioritize graft allocation to HCC candidates.

Method: Waitlist information and status of candidates listed during the period 1/10/2009–14/8/2015 is

retrieved from the Hong Kong Organ Registry & Transplant System to calculate the waitlist outcomes (liver transplant, dropout, removal, alive waiting) for HCC and non-HCC candidates. All adult candidates over the age of 18 listed for all indications are included. Waitlist outcomes are compared between candidates with and without HCC. Student's t test is used to compare between means. z-score test is used to compare between proportions. Person correlation test is used for determine correlation between continuous linear variables.

Result: One hundred and forty-one HCC candidates is compared with 289 non-HCC candidates. Eighty-eight (62%) HCC candidates received MELD exception score of 18 or above. Significantly higher proportion of HCC candidates with MELD exception received liver transplant during the period compared to non-HCC candidates (60.3% vs. 45%, $p = 0.01$); while there is no significant different in dropout rate between HCC and non-HCC candidates (25% vs. 28.4%, $p = 0.5$). Further analysis showed that seasonal variation in graft supply is weakly but significantly correlated to dropout rate of non-HCC candidates but not to that of HCC candidates ($R^2 = 0.336$, $p = 0.003$ vs. $R^2 = 0.08$, $p = 0.181$).

Conclusion: HCC candidates with MELD exception are over-advantaged in liver graft allocation under the current prioritization scheme.

0106

Long-Term Outcomes of Liver Transplantation for Hepatocellular Carcinoma: The Singapore National University Hospital Experience

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Objectives: Liver transplantation has been well established as an effective treatment for hepatocellular carcinoma (HCC) with the Milan criteria (1 nodule <5 cm or 2–3 nodules each <3 cm, no extrahepatic spread or macrovascular invasion) considered as the gold standard criteria to achieve excellent long term outcomes. Among various expanded criteria, the University of California San Francisco (UCSF) criteria (1 nodule <6.5 cm, or 2–3 nodules each <4.5 cm with total tumor diameter <8 cm, no extrahepatic spread, no macrovascular invasion) is well validated and widely acceptable. We report the long-term outcomes of HCC transplanted according to these criteria in our centre.

Method: This is a single liver transplant centre observational study. All consecutive adult liver transplantation cases in our centre from 1996 to 2015 were enrolled. Baseline demographics, clinical parameters, HCC tumor characteristics and long-term outcomes were recorded. Categorical and

continuous data were analysed with Fisher-exact and Mann Whitney U test, respectively. Survival analysis was estimated with Kaplan-Meier curve. Outcome predictors will be determined with multivariable logistic regression.

Results: Between 1996 to 2015, 177 adult liver transplantation were performed in our centre, of which 141 cases had sufficient data for analysis. Mean age was 52 years old, 113 cases (80%) were males, 56 cases (40%) were HBV, mean MELD was 17 and median follow-up was 40 months. Sixty-four cases (45%) had HCC, of which 55 (89%) were UCSF-In and 7 (11%) were UCSF-Out. Overall post-transplant HCC recurrence rate was 12.5%. Overall 1, 3 and 5-year survival for all patients were 90%, 84% and 78%, respectively. Among non-HCC cases, overall 1, 3 and 5-year survival were 95%, 90% and 90%, respectively. For UCSF-In and UCSF-Out HCC cases, overall 1, 3 and 5-year survival were 87%, 79%, 70%; and 86%, 67% and 40%, respectively.

Conclusions: Close to half of liver transplantation cases in our centre were performed for HCC. Long-term transplant outcomes of UCSF-In HCC cases were excellent with acceptable recurrence rate. However, overall 5-year survival for UCSF-Out HCC cases was low at 40%.

0112

Wide Resection Margin Improves Survival in Patients with Early Intrahepatic Cholangiocarcinoma – A 22-Year Single Center Experience

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Objectives: Prognosis of Intrahepatic Cholangiocarcinoma (ICC) remained poor despite the multitude advancement of medical care. Resection margin status is one of the few modifiable factors that a surgeon could possibly manipulate to alter the disease outcome. However, the significance of margin status and margin width is still controversial. This study serves to further elucidate the role of them.

Method: This is a retrospective cohort from the Queen Mary Hospital, The University of Hong Kong. Consecutive patients diagnosed to have ICC and with surgical resection performed in curative intent were retrieved, while patients with cholangiohepatocellular carcinoma, Klaskin tumour, tumour of extrahepatic bile duct and uncertain tumour pathology were excluded.

Results: From 1991 to 2013, there were 107 patients underwent hepatectomy for ICC. Gender predilection was not observed with 58 males and 49 females, median age of the patients was 61. The median tumour size was 6 cm and most of them (43%) were moderately differentiated adenocar-

cinoma. Clear resection margin were achieved in 95 patients (88.8%) and the median margin width was 0.5 cm. The Hospital length of stay and operative mortality were eleven days and 3% respectively. The disease free survival and overall survival was 17.5 months and 25.1 months respectively. Multivariate analysis showed that margin width was an independent factor associated with disease free survival ($P = 0.015$, 95% C.I. 0.4–0.9). Sub-group analysis in patients with solitary tumour showed that margin width is an independent factor affecting overall survival ($P = 0.048$ OR 0.577 95% CI 0.334–0.996). Discriminant analysis showed that the overall survival increased from 36 months to 185 months when margin width was greater than 0.9 cm ($p = 0.025$) in patients with solitary tumour.

Conclusion: Aggressive resection to achieve resection margin of at least 1 cm maximizes chance of cure in patients with early ICC.

Oncology

0020

The Examination of the Factors Associated to the Response of DEB-TACE for Hepatocellular Carcinoma

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Aim: Transarterial chemoembolization using a drug-eluting bead (DEB-TACE) for hepatocellular carcinoma (HCC) was introduced in 2013 in Japan and widely used in the present. In this study we examined the factors associated to the response of DEB-TACE for hepatocellular carcinoma.

Method: 83 patients (M:F = 66:17, age (median) 73, Child A:B:C = 50:31:2, BCLC stage A:B:C:D = 2:59:10:2) with unresectable HCC who received DEB TACE in our hospital were studied. DEB TACE procedures using HepaSphere eluting CDDP in 44 sessions and DC Bead eluting epirubicin in 39 sessions were performed. The objective radiological response was classified according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) v.1.1 by dynamic CT at one month after therapy. Adverse events were evaluated using NCI CTCAE v. 4.03. These 83 HCC cases were classified into 4 types as simple nodular type, simple nodular type with extranodular growth, confluent multinodular type, diffuse type according to the simple gross classification by two radiologists according to the shape of early stain or defect of delay phase of dynamic CT before DEB-TACE.

Results: The imaging response was assessed in each session as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) in 2 (2.4%), 29 (34.9%), 32 (38.6%), and 15 (18.1%) respectively. Objective response rate was 37.3% and disease control rate was 75.9%. Tumor factors associated response found to be significant on univariate analysis were existence of the capsular, simple gross classification (simple nodular type), number of tumor (≤ 3).

Conclusion: Existence of the capsular, simple gross classification (simple nodular type), number of tumor (≤ 3) were found to be associated for the response of DEB TACE in patients with unresectable HCC.

0023

Phase II Study of the c-Met Inhibitor Tepotinib Compared with Sorafenib as First-Line Treatment for Asian Patients with Advanced HCC

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Background [AN1] and Objectives: Patients with advanced HCC have a poor prognosis, particularly if c-Met is amplified or overexpressed. Current first-line therapy is sorafenib, which has limited efficacy and is not widely used in Asia. We are conducting a phase Ib/II trial of first-line tepotinib, a highly selective inhibitor of c-Met (NCT01988493), in Asian patients with advanced HCC. In the phase Ib part, tepotinib was well tolerated at doses up to 1,000 mg once-daily and no dose-limiting toxicities were reported (Qin et al. ECC 2015, abstract 2353). The most frequently occurring treatment-related grade 3/4 adverse event was lipase increase (13%). Six patients had c-Met-positive tumors at the time of analysis: 1 had a best overall response of partial response and 3 had stable disease. We describe the design of the ongoing phase II part of the trial in which first-line tepotinib 500 mg once-daily, the selected recommended phase II dose, is being compared with sorafenib in Asian patients with c-Met-positive HCC.

Trial Design: The phase II part is a randomized, open-label, active-controlled trial being conducted at 30+ sites in Asian countries including China, Taiwan, and South Korea. Eligible patients have: histologically/cytologically confirmed advanced HCC of Barcelona Clinic Liver Cancer Stage C; ECOG

performance status ≤ 2 ; Child-Pugh Class A liver function without encephalopathy; and no prior systemic therapy for HCC. Patients are required to have c-Met-positive tumors, defined as $\geq 50\%$ of tumor cells having moderate (2+) or strong (3+) c-Met staining by immunohistochemistry.

A planned 140 patients will be randomized to receive first-line tepotinib 500 mg once-daily or sorafenib 400 mg BID q21d. The sample size provides 80% power with a two-sided significance level of 10% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio of 0.6. Therapy is administered until disease progression, intolerable toxicity, or withdrawal of consent. The primary endpoint is independently assessed time to progression (TTP). Secondary endpoints include investigator-assessed progression-free survival and TTP, overall survival, objective response, and tolerability. Exploratory endpoints include biomarkers of tepotinib activity and patient prognosis, and patient-reported outcomes assessed using Functional Assessment of Cancer Therapy Hepatobiliary (FACT-HP).

This phase II study will indicate whether tepotinib has the potential to improve treatment outcomes for patients with c-Met-positive HCC compared to the current standard of care, sorafenib.

0029

Association of Serum Levels of Transforming Growth Factor $\beta 1$ with Disease Severity in Egyptian Patients with HCC

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Background: TGF is overexpressed by tumor cells like other proteins and growth factors. TGF- $\beta 1$ is then activated in the extracellular compartment but is unable to control cell proliferation because of the absence or low level of TGF- $\beta 1$ receptors on the plasma membrane of malignant hepatocytes. This potential mechanism might interrupt the autocrine regulation loop of TGF- $\beta 1$ and its blocking effect on cell proliferation. TGF is overexpressed by tumor cells like other proteins and growth factors. TGF- $\beta 1$ is then activated in the extracellular compartment but is unable to control cell proliferation because of the absence or low level of TGF- $\beta 1$ receptors on the plasma membrane of malignant hepatocytes. This potential mechanism might interrupt the autocrine regulation loop of TGF- $\beta 1$ and its blocking effect on cell proliferation. Transforming growth factor $\beta 1$, is a multifunctional cytokine involved in the regulation of growth and differentiation of both normal and transformed cells. It was found that TGF $\beta 1$ mRNA and its

proteins were overexpressed in HCC tissues and its plasma levels were elevated in HCC patients, however, the exact role in development and prognosis of HCC remains unclear.

Aim: To study the association of serum levels of TGF β 1 with disease severity in patients with HCC.

Material and Methods: A total of 180 Egyptian subjects were classified into 6 groups:

Group 1: 30 patients with an early stage HCC (BCLC stages 0 & A).

Group 2: 30 patients with an intermediate stage HCC (BCLC stage B).

Group 3: 30 patients with an advanced stage HCC (BCLC stage C).

Group 4: 30 patients with a terminal stage HCC (BCLC stage D).

Group 5: 30 cirrhotic patients without HCC.

Group 6: 30 control subjects.

Demographic, clinical, laboratory and radiological characteristics of all subjects were evaluated; Barcelona Clinic Liver Cancer (BCLC) stage was identified in all patients with HCC. Serum levels of TGF β 1 were measured by an ELISA technique. Statistical analysis was done using SPSS software.

Results: Serum levels of TGF β 1 were significantly higher in patients with HCC (1687.47 ± 1462.81 pg/ml) than cirrhotics (487.98 ± 344.23 pg/ml, $p < 0.001$) and control subjects (250.16 ± 284.61 pg/ml, $p < 0.001$). Serum TGF β 1 in BCLC stage A patients (652.83 ± 1084.60 pg/ml) was significantly lower than that in BCLC stage C patients (2150.68 ± 1970.10 pg/ml, p value 0.004) and BCLC stage D (1668.78 ± 1628.15 pg/ml, p value 0.038).

Conclusions: Serum levels of TGF β 1 may have a role in tumor growth and progression and could be used for risk prediction of HCC in cirrhotic patients.

controversial. The aim of this study was to evaluate metformin's effect on clinical outcomes in diabetic patients with pancreatic cancer treated with curative resection.

Methods: We designed a nationwide population-based study. Data were provided from the Korea Central Cancer Registry and the National Health Insurance Service in the Republic of Korea. The study cohort consisted of 28,862 patients newly diagnosed with pancreatic cancer between 2005 and 2011. Metformin exposure was determined from prescription information from 6 months before the first diagnosis of pancreatic cancer to last follow-up. The main outcome was cancer-specific survival. Survival analyses were conducted using Kaplan-Meier methods and Cox proportional hazards model. Dose-response analyses were carried out using cubic spline regression model. All statistical tests were two-sided.

Results: A total of 764 patients underwent curative resection, met none of the exclusion criteria, and were prescribed oral hypoglycemic agents. The cancer-specific survival (5-year, 31.9% vs. 22.2%, $p < 0.001$) was significantly higher in the 530 metformin users than in the 234 diabetic metformin non-users. After multivariable adjustments, metformin users had significantly lower cancer-specific mortality as compared with metformin non-users (hazard ratio, 0.727; 95% confidence interval, 0.611–0.868). Cubic spline regression analysis demonstrated significantly decreased cancer-specific mortality with increasing dose of metformin ($p = 0.0047$).

Conclusions: This large study indicates that metformin may decrease cancer-specific mortality rates in diabetic pancreatic cancer patients receiving curative resection, independently of other factors, with a dose-response relationship.

0032

Association between Metformin Use and Mortality in Patients Receiving Curative Resection for Pancreatic Cancer: A Nationwide Population-Based Study

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Background and Objectives: Preclinical studies support an antitumor effect of metformin. However, clinical studies have conflicting results and metformin's effect remains

0040

The Advantage of Cholangioscopy with Narrow-Band Image in Hepatobiliary Malignant Tumors

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Background: Narrow-band image (NBI) makes it possible a high-contrast observation of mucosal structures and vascular patterns in gastrointestinal tract diseases. Recently, cholangioscopy with NBI using percutaneous approach has been used as a diagnostic modality for better visualization in hepatobiliary malignant tumors, however, there are few reports on it. Our aim is to evaluate the advantage of cholangioscopy with NBI using percutaneous approach in hepatobiliary malignant tumors.

Patients: Between January 2006 and December 2015, 256 cholangioscopies using percutaneous approach were conducted in total 211 patients. Among these, 60 patients were suspicious of hepatobiliary malignant tumors. Eighteen patients with an ambiguous margin on endoscopic retrograde

cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) of them, to whom NBI tipped the balance in diagnosis of lesion and decision of lesion extent by adding NBI, were involved in our study.

Results: The mean age of 18 patients was 62.7 (± 10.3) years old. They included 10 men and 8 women. Underlying diseases were all malignant in 18 patients (16 bile duct cancers, 1 liver cancer, 1 pancreas cancer with common bile duct invasion). In 10 cases with papillary type tumor, minute superficial spreading tumor was detected by NBI more easily, and NBI provided a better visualization of tumor vessel and margin evaluation in 5 cases with infiltrative type tumor. In 3 cases with mucin-hypersecreting tumor, NBI showed better penetration through the mucin and give us a better clear image.

Conclusion: In conclusion, cholangioscopy with NBI using percutaneous approach is very useful for evaluation of suspected hepatobiliary malignant tumors with an ambiguous margin on ERCP or MRCP. It can give us an accurate pathologic mapping, and this information seems to be essential before deciding a treatment strategy.

0049

The Efficacy, Toxicities and Prognostic Factors of Stereotactic Radiotherapy in BCLC Stage C Hepatitis B Related Hepatocellular Carcinoma

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Objectives: To study the role of stereotactic body radiotherapy (SBRT) in patients with Barcelona Clinic Liver Classification (BCLC) stage C, Hepatitis B (HBV) related hepatocellular carcinoma (HCC).

Methods: Thirty-two consecutive and eligible patients who were treated with fractionated SBRT between January 2008 and December 2010 were analysed. The average gross tumor volume was 765 cm³. The treatment prescription ranged from 20–40 Gy (median, 32 Gy) in 5–10 fractions over 1–2 weeks. Radiotherapy was planned by 4-dimensional CT and under image guidance. Isocentre was verified by ExacTrac stereotactic body setup system (BrainLab, Ltd). Pre-SBRT surgical resection or radiofrequency ablation, and TACE were given in 25% and 62.5% of patients, respectively. Sorafenib was given to 18.7% and 15.6% of patients before and after SBRT, respectively. The survival, response rate, toxicities, clinical and dosimetric parameters were evaluated, and multivariate analysis was performed to identify the significant predictors of survival.

Results: Median follow-up was 13.4 months; median survival of was 13.3 months (95% CI 11.4 m to 15.2 m), with 1-year and 3 year actuarial survival 62.5% (95% CI 54% to

71%) and 14.1% (95% CI 7.7% to 20.5%), respectively. Tumor Response rate by RECIST criteria was 69%. 89% patients were asymptomatic (grade 0) during radiotherapy except 11% patients had grade 2 fatigue and 3% patients had grade 2 nausea and vomiting. None of them had grade 3 or above toxicities, including HBV reactivation, chronic hepatitis B exacerbation or radiotherapy induced liver disease within 3 months after SBRT. AFP reduction at 3 months or more after radiotherapy ($p < 0.041$) and gain in body weight after SBRT ($p < 0.0001$) were significantly associated with longer survival after multivariate analysis.

Conclusions: SBRT with individualized dose up to 40 Gy in 10 fractions can be delivered safely to large (average GTV >700 cm³) BCLC stage C HBV related HCC patients. The survival rate of SBRT in this study was better than that of systemic therapy reported in the literature (median survival, 13.3 months vs. 10.7 months). AFP reduction for 3 months or more and body weight gain after radiotherapy were prognostic factors for longer survival. More prospective studies are warranted to confirm these results.

0052

Radiofrequency Ablation versus Stereotactic Body Radiotherapy for Small Hepatocellular Carcinoma: A Markov Model-Based Analysis

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Background and Objective: There is growing interest in the application of SBRT for HCC treatment. However, there have been no randomized controlled trials comparing SBRT with standard treatments such as RFA. The purpose of this study is to compare radiofrequency ablation (RFA) with stereotactic body radiotherapy (SBRT) for patients with hepatocellular carcinomas (HCC) smaller than 3 cm.

Methods: A Markov cohort model was developed to simulate a cohort of patients aged 60–65 years with small HCCs who had undergone either RFA or SBRT and were followed up over their remaining life expectancy. The inclusion criteria were: (i) any solitary HCC ≤ 3 cm in diameter with \leq three nodules; (ii) absence of extrahepatic metastasis or portal/hepatic vein invasion; (iii) Child-Pugh Class A or B. Twenty thousand virtual patients were randomly assigned to undergo RFA or SBRT.

Results: Predicted life expectancy was 6.452 and 6.371 years in the RFA and SBRT groups, respectively. The probability distributions of the expected overall survival were nearly identical. The 95% confidence intervals were 6.25–6.66 and 6.17–6.58 years for RFA and SBRT, respectively. The difference between RFA and SBRT was insignificant ($P = 0.2884$). Two-way sensitivity analysis demonstrated that if

the tumor is 2 to 3 cm, SBRT is the preferred treatment option.

Conclusions: Our Markov model has shown that expected overall survival of SBRT is nearly identical to RFA in HCCs smaller than 3 cm, but SBRT may have an advantage for tumors 2 cm and larger. A randomized trial is required to confirm these findings.

0062**Analysis of Sorafenib Outcome in Patients with Hepatocellular Carcinoma: Focusing on the Clinical Course**

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Background: There are various clinical processes involved before starting sorafenib therapy. Treatment outcomes of sorafenib therapy may greatly vary depending not only on tumor spread but also on clinical processes prior to sorafenib therapy and timing of sorafenib administration in the clinical course of hepatocellular carcinoma (HCC). The goals of this study were as follows: (1) to characterize and assess sorafenib-treated patients focusing on stage progressing processes from initial diagnosis prior to sorafenib therapy and (2) to compare data of intermediate-stage patients receiving TACE who are switched from TACE to sorafenib therapy before and after progressing to advanced-stage HCC, respectively.

Methods: Patients with HCC treated with sorafenib as a first-line chemotherapy were retrospectively analyzed. We only included patients with clinical courses documented from the time of the initial diagnosis.

Results: Of 123 patients started on sorafenib therapy at the advanced-stage, 56 patients (46%) were initially diagnosed with advanced-stage HCC, 38 patients (31%) progressed to the advanced-stage HCC through the intermediate-stage, and 29 patients (24%) progressed to advanced-stage HCC directly from the early-stage. Patients directly progressing from early-stage HCC had the highest rate of HCV infection (69%) compared with the proportion of patients diagnosed with the advanced-stage (25%) and those who progressed through the intermediate-stage (45%) ($P < 0.001$). The majority (75%) of patients initially diagnosed with advanced-stage HCC had intrahepatic MVI. Hence, the status of intrahepatic lesions significantly differed among the three groups ($P < 0.001$). Overall survival (OS) in patients progressed directly from the early stage (15.3 months) was significantly longer than that in patients diagnosed at the advanced-stage (5.3 months, $P = 0.022$) and progressed from the intermediate-stages (6.0 months, $P = 0.041$). Of 105 patients diagnosed at the intermediate-stage, OS

from the time of starting sorafenib therapy before progression to the advanced-stage (67 patients) was significantly longer than for patients starting sorafenib therapy only after progression to the advanced-stage (38 patients) ($P = 0.015$).

Conclusion: Characteristic differences between stage progression processes might affect prognosis in advanced-stage HCC patients. Switching to sorafenib therapy before progression to the advanced-stage appears more effective than switching after progression to the advanced-stage in intermediate-stage HCC patients.

0064**Combined Transarterial Chemoembolization (TACE) and Stereotactic Body Radiotherapy (SBRT) in HKLC Intermediate and Locally Advanced Hepatocellular Carcinoma (HCC)**

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Purpose: To describe the outcome of SBRT combined with TACE in inoperable intermediate (HKLC stage IIb-IIIa) & locally advanced (HKLC stage IIIb) HCC. We also evaluate the prognostic factors of clinical outcome.

Materials and Methods: During the period of 2008 to 2015, 64 consecutive intermediate ($n = 38$) and locally advanced ($n = 26$) HCC patients that are unsuitable for surgical resection, were treated with single dose of TACE followed by SBRT 3–6 weeks later in our center; their outcomes were prospectively monitored. Those who had Child-Pugh (CP) score $> B7$, ECOG ≥ 2 , extra-hepatic metastasis or infiltrative tumors were excluded in this analysis. SBRT dose, range from 5–8Gy x 6 fractions or 4Gy x 5–10 fractions, were individualized according to normal tissue constraints. Resections were carried out in 12 patients (18.8%) after downsizing of tumor, otherwise no scheduled treatment delivered unless disease progression. Primary end point was overall survival. Secondary end points were response rate and toxicity.

Results: Median follow-up time was 17.9 months (range: 3–96 months). Patients' characteristics were as follows: CP class A/B ($n = 60/4$); HKLC stage IIb/IIIa/IIIb ($n = 34/4/26$); BCLC stage B/C ($n = 39/25$); solitary/oligonodular (2–3)/multinodular (>3) ($n = 35/20/9$); tumor size 5–10 cm/10.1–15 cm/ >15 cm ($n = 30/19/15$); vascular invasion ($n = 18$). The median overall survival (OS) was 23.2 months (95% CI, 15.1–38.6 months). For intermediate (HKLC stage IIb and IIIa) and locally advanced (HKLC stage IIIb) tumor, the median OS was 23.7 months (95% CI: 19.8–42.3 months) and 16.9 months (95% CI: 7.6–26.1 months) respectively, the latter compares favorably to historical data of around 6 months.

Conversion to resectable tumor after TACE + SBRT (HR = 10.3, 95% CI 2.7–39.1) and size of lesion (HR = 4.25, 95% CI 2.04–8.84) were significant on multivariate analysis in predicting OS. The objective tumor response rate by RECIST criteria was 68.9%. All except one patient (98.4%) completed the planned treatment. Toxicity \geq grade 3 was seen in 17.2% of patients, and treatment-related death occurred in two patients (3.1%). 11% of patients without disease progression had decline of CP class at 3 months. No patient developed classical radiation-induced liver disease (RILD).

Conclusion: Combined TACE and SBRT is an effective and safe treatment in HKLC intermediate or locally advanced HCC that unsuitable for resection. Overall survival is remarkably better than historical data in locally advanced tumor (HKLC stage IIb). Further prospective studies on this approach are warranted.

0067

Results of TRACER: A Phase II Randomized, Double-Blinded, Multicenter Asian Study Investigating the Combination of Transcatheter Arterial Chemoembolization (TACE) and Oral Everolimus in Localised Unresectable Hepatocellular Carcinoma (HCC)

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Background and Objectives: Preclinical data indicated that combining everolimus with TACE may enhance the effect of local chemoembolization by downregulating pathways contributing to resistance (HIF-1 α and VEGF) and increasing sensitivity to chemocytotoxic agents. Therefore, the primary objective of this study was to evaluate the anti-tumor effect, measured by time to progression (TTP), of everolimus plus

TACE versus TACE alone. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Method: Adults with newly diagnosed, localized, unresectable HCC were randomized (1:1) to receive in a double-blind manner TACE (doxorubicin and DC Bead[®]) plus everolimus 7.5 mg/day or placebo. Patients were stratified by Barcelona Clinic Liver Cancer (BCLC) staging and country. Key eligibility criteria included: suitable for palliative local TACE treatment, cirrhotic status of Child-Pugh Class A with no encephalopathy and with no evidence of main portal invasion or extrahepatic metastasis. Patients were excluded if prior treatment had included mTOR inhibitors.

Results: Of the planned 80 patients, 59 were randomized (33 to everolimus+TACE; 26 to placebo+TACE). Mean age was 60 years. All patients were Asian and 81% were male. Disease stage based on BCLC was B for the majority of patients (86%). Time since initial diagnosis for all patients was \leq 12 months. Hepatitis was the most common HCC etiology: hepatitis B in 63%, hepatitis C in 25%. Given the early termination of recruitment, only 50 disease progression events occurred (25 events in each arm) as opposed to the expected 60. Median TTP was 6.3 months for everolimus and 6.4 months for placebo (HR = 0.934, 90% CI: 0.573 to 1.524). ORR was lower for everolimus compared with placebo (42% versus 54%) but DCR was higher (91% versus 77%). Median OS was higher for everolimus (30 months) compared with placebo (22 months) but was not statistically significant (HR = 0.949, 90% CI: 0.518 to 1.739). Abdominal pain and pyrexia were the most common AEs in patients from both groups and occurred at higher rates in the placebo group. Decreased appetite, mouth ulceration, stomatitis and thrombocytopenia were more common in the everolimus group. More patients in the everolimus group experienced severe or life-threatening AEs (48.5% versus 30.8%) with thrombocytopenia and pneumonia occurring most frequently.

Conclusion: The efficacy of everolimus plus TACE in localized unresectable HCC did not appear to be superior to TACE alone. The combination was tolerable, with everolimus related AEs consistent with the known safety profile. However, the study is inconclusive as it was underpowered.

0073

Distribution of Peripheral Blood Lymphocytes in Patients with Advanced Hepatocellular Carcinoma (HCC) Who Received Lenalidomide Treatment

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Background: Lenalidomide has both immunomodulatory and anti-angiogenic activities. We explored the association between distribution of peripheral blood lymphocyte subsets and clinical outcome in patients with advanced HCC who received lenalidomide treatment.

Methods: Peripheral blood of patients who were enrolled in a single-arm phase 2 clinical trial of lenalidomide as second-line therapy for advanced HCC was collected before and 14 days after study treatment. All patients received lenalidomide 25 mg/day lenalidomide on days 1–21 every 4 weeks. Tumor response was assessed according to RECIST1.1 after 4 and 8 weeks of treatment and every 8 weeks thereafter. The distribution of peripheral blood lymphocyte subsets was measured using fluorescence-activated cell sorting and then examined their associations with the treatment outcomes.

Results: Fifty-five patients (M/F: 45/10, median age 59.8 years) were enrolled. The overall response rate (RR) was 13% (0 complete and 7 partial responses; 22 durable [≥8 weeks] stable disease), and the disease control rate (DCR) was 53%. The median PFS and overall survival (OS) was 1.8 and 8.9 months, respectively. Significant ($p < 0.01$) changes after lenalidomide treatment was found in the mean percentage of B cells (9.8% to 7.0%), naïve CD4 T cells (11.0% to 6.4%), and regulatory T cells ($3.4E-6$ to $5.0E-6$). None of the aforementioned changes was associated with treatment outcome. Patients with a high (> median) percentage of B cells before lenalidomide treatment, had higher disease control rate (70% vs. 36%, $p = 0.010$) and longer PFS (median, 3.6 vs. 0.9 months, $p < 0.001$) and OS (median, 9.5 vs. 7.1 months, $p = 0.042$).

Conclusions: Lenalidomide had promising anti-tumor activity in HCC. The pre-treatment B cell percentage and other potential immune-related biomarkers are worthy of further exploration.

0080

Clinical Outcomes of Definitive or Salvage Stereotactic Body Radiotherapy for Hepatocellular Carcinoma

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Background and Objectives: To investigate the efficacy and safety of stereotactic body radiation therapy (SBRT) in hepatocellular carcinoma (HCC) and evaluate the prognostic factors for progression-free (PFS) and overall survival (OS) in HCC patients who received the definitive or salvage SBRT.

Methods: The records of 27 HCC treated with definitive or salvage SBRT between 2012 and 2015 were analyzed retrospectively in single institution. The dose of 45–60 Gy in 3–6 fractions was prescribed according to tumor size and liver volume. Most tumor lesions but one received previous treatment such as TACE or RFA. Treatment responses were evaluated according to modified RECIST criteria.

Results: The median follow-up period was 16 months (range, 3–46). Median age was 66 years (range, 42–77). All patients were classified as Child-Pugh A. Most of patients (88.9%) were HBV or HCV carrier. Twenty-two (91.5%) patients had BCLC stage A disease, 4 (14.8%) had stage B disease, and 1 (3.7%) had stage C disease. Median level of AFP prior to SBRT was 8 ng/ml (range, 2–3766 ng/ml). Number of viable tumor before SBRT was 0 in 11 patients (40.8%), 1 in 10 patients (37.0%), and 2 in 6 patients (22.2%). Median tumor size was 2 cm (range, 1–5 cm). Median RT dose was 112.5 Gy10 (range, 85.5–180 Gy10). Non-classic radiation-induced liver disease was observed in 2 patients (7.4%). Grade 2 chest wall pain was developed in 2 patients (7.4%) due to radiation related rib fracture. After SBRT, complete response (CR) was observed in 21 (77.8%), partial response (PR) in 1 (3.7%), stable disease (SD) in 3 patients (3.7%) and disease progression (DP) in 2 (7.4%) patients. OS rates at 1 and 2 years were 92.6% and 65.4%, respectively. Median survival time was 42 months. PFS rates at 1 and 2 years were 47.6% and 41.7%, respectively. Median PFS time was 10 months. On multivariate analysis for PFS, SBRT response (CR or PR versus SD or DP, Hazard ratio (HR) 0.21, 95% confidence interval (CI) 0.046–0.98, $p = 0.047$) and AFP level prior to SBRT (≤ 200 ng/ml versus > 200 ng/ml, HR 0.089, 95% CI 0.016–0.489, $p = 0.005$) were significantly associated with PFS.

Conclusions: Despite small number of patients, our findings demonstrated that SBRT is a safe and effective treatment for HCC with acceptable local control rates and low treatment-related toxicity. Poor SBRT response and higher AFP level prior to SBRT were the independent adverse prognostic factor for PFS.

0082

A Randomized, Double-Blind, Placebo-Controlled Phase III Study of Ramucirumab versus Placebo as Second-Line Treatment in Patients with Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein Following First-Line Sorafenib (REACH-2)

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Ramucirumab (RAM) is a humanized IgG1 monoclonal antibody that inhibits VEGF-A, C and D activation of the vascular endothelial growth factor receptor (VEGFR2). The Phase III REACH study assessed RAM versus placebo (PBO) in the treatment of patients with advanced hepatocellular carcinoma (HCC) after prior sorafenib. Significant improvements in overall survival (OS) in the overall population (N = 565) was not achieved (Hazard Ratio [HR] = 0.865; 95% CI 0.717–1.046; p = 0.1391). However in the pre-specified subgroup of patients with baseline alpha-fetoprotein (AFP) \geq 400 ng/ml (N = 250), clinically meaningful and significant improvements in OS (HR = 0.674; 95% CI 0.508–0.895; p = 0.0059), PFS (HR = 0.699; p = 0.0106) and ORR (6.7% RAM vs. 0.8% PBO; p = 0.0254) were observed. No OS treatment benefit was observed in patients with a baseline AFP level <400 ng/ml (N = 310) (HR = 1.093; 95% CI 0.836–1.428; p = 0.5059). Comparing the OS results in patients with baseline AFP \geq and <400 ng/ml, the subgroup-by-treatment interaction was significant (p = 0.0272). The safety profile of RAM was considered manageable. In patients with AFP \geq 400 ng/ml, a strong trend for delay in symptom deterioration (p = 0.054) and delay in performance status (PS) deterioration (p = 0.057) was observed in patients treated with RAM compared to PBO.

REACH-2 is a randomized, double-blind, placebo-controlled phase III study of RAM versus PBO in patients with HCC and elevated baseline AFP following prior sorafenib therapy. Eligible patients are randomized 2:1 to receive RAM (8 mg/kg, IV) or placebo on Day 1 of each 14-day cycle until disease progression or other discontinuation criteria. Eligible patients must have a diagnosis of HCC (tissue or tumor with classical imaging characteristics); prior sorafenib \geq 2 weeks; Child-Pugh score of 5 or 6; Barcelona Clinic Liver Cancer Stage C or Stage B disease not amenable to or refractory to locoregional therapy; AFP \geq 400 ng/ml; and ECOG PS of 0–1. Patients with history of encephalopathy, clinically meaningful ascites,

liver transplant, or hepatic locoregional therapy after sorafenib are not eligible. The primary objective is to assess the OS for patients treated with RAM versus PBO. Target enrollment is 399 patients with the final analysis at 318 events (20% censoring). Secondary objectives include progression free survival, objective response rate, safety, and patient focused outcomes including evaluations using the Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index (FHSI-8) and EuroQol-5 Dimension (EQ-5D) instrument. Additional objectives include assessment of biomarkers relevant to angiogenesis and HCC. NCT02435433.

0083

High-Dose Radiotherapy Using Hypofractionation for Moderate-Sized Hepatocellular Carcinoma: Analysis with Universal Survival Curve Model

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Objectives: The aim of this study was to compare the clinical outcome of hypofractionated radiotherapy (HRT) and stereotactic body radiotherapy (SBRT) for unresectable moderate-sized hepatocellular carcinoma (HCC) using the universal survival curve (USC) data from a clonogenic assay of in human hepatocellular carcinoma cell lines.

Methods: Three human hepatocellular carcinoma cell lines (HepG2, Huh7 and SKHep1) were used and cell survival was determined by a clonogenic assay. Based on these data, the equivalent dose functions including biological equivalent dose (BED), single fraction equivalent dose (SFED), and standard effective dose (SED) for each dose-fractionation schedule of 72 patients with unresectable HCC ranging in size from 5 cm to 10 cm were calculated using USC model. Radiotherapy were delivered with HRT (10 fractions) or SBRT (3–5 fractions), in three institutions from 2003 to 2013. The total radiation doses ranged from 33 Gy to 60 Gy in 3 to 10 fractions.

Results: The α/β ratio of hepatocellular carcinoma cell lines using universal survival curve was experimentally determined to be 8.33 Gy. The transition dose (D_T) was calculated to be 7.60 Gy. Median values of SFED, BED and SED for all study patients were 21.6 Gy (range, 14.9–53.6), 125.0 Gy, (range, 59.2–318.9) and 118.9 Gy (range, 40.8–257.1), respectively. The median follow-up period after radiotherapy was 12.8 months. The overall response rate at 3 month after radio-

therapy was 52.8% (complete response: 4.2%; partial response: 48.6%). The local control rates at 1- and 2-years were 75.1% and 65.1%, respectively. The overall survival (OS) rates at 1- and 2-years were 70.1% and 45.2%, respectively, with a median survival of 21 months. In univariate analysis, the SFED, and SED were identified as significant prognostic factors for OS. The optimal cutoff values were 35.6 Gy for SFED, 205.0 Gy for BED, and 165.3 Gy for SED.

Conclusions: This study demonstrated that high-dose RT using HRT or SBRT, for moderate-sized HCC can be safely delivered and showed feasibility with substantial tumor regression and survival and the equivalent dose derived from the USC model were identified as significant prognostic factors for survival.

0096

Prognostic Value of Preoperative Alpha-Fetoprotein (AFP) Level in Patients Receiving Curative Hepatectomy

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Objectives: The value of alpha-fetoprotein (AFP) as a prognostic indicator in patients with hepatocellular carcinoma (HCC) has been proposed in recent studies, but the evidence so far is still contradictory. This analysis aims to evaluate the prognostic value of preoperative AFP level in patients undergoing curative resection.

Method: This retrospective study reviewed the prospectively collected data of all patients who underwent initial liver resection for HCC at Queen Mary Hospital during the period from March 2004 to March 2013. Patients with palliative resection, positive margin after pathological examination or distant metastasis were excluded from the study. Survival of patients with AFP level of <20, 20–400 and >400 ng/ml were compared with Kaplan-Meier analysis. Subgroup analysis was performed according to tumour stage (7th edition UICC staging) and tumour size. The optimal cutoff value was determined by discriminant analysis.

Results: A total of 842 patients were included. Best overall and disease free survival was observed in patients with AFP level <20 ng/ml. Progressively worse outcomes were seen for patients with increasing level of AFP. The median overall survival were 132.9, 77.2 and 38.4 months for patients with AFP <20, 20–400 and >400 ng/ml respectively ($p < 0.001$). The median disease free survival for these three groups were 55.6, 25 and 8.4 months respectively ($p < 0.001$). There was significant difference in both overall and disease free survival among all 3 groups. With subgroup analysis according to tumour stage (stage I and II versus stage III and IV) and tumour size (5 cm or less versus larger than 5 cm), such difference was still observed

and remained statistically significant. Optimal cutoff value by discriminant analysis was 12918.3 ng/ml for overall survival and 9733.3 ng/ml for disease free survival.

Conclusions: This study demonstrates that AFP is a significant prognostic indicator in HCC. Despite tumour stage and size, high level of AFP is associated with poorer overall and disease free survival. Whether the level of AFP should be included in current staging systems, or treatment protocols, is yet to be determined.

0099

Risk Stratification for Locally Advanced Hepatocellular Carcinoma Using Double Biomarkers: Clinical Significance of Pretreatment Alpha-Fetoprotein and ¹⁸F-FDG PET

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Objectives: We investigated the significance of ¹⁸F-fluoro-2-deoxyglucose ¹⁸FDG-positron emission tomography (¹⁸F-FDG PET) parameters and alpha-fetoprotein (AFP) in patients with locally advanced hepatocellular carcinoma (LA-HCC).

Methods: We retrospectively analyzed data on 228 patients with LA-HCC, who underwent pretreatment ¹⁸F-FDG PET between January 2003 and December 2013. All patients were treated using liver-directed therapy involving radiotherapy (RT). Maximum maximal standardized uptake values (SUV) and the tumor to normal liver ratios of the SUV were calculated and pretreatment AFP value was obtained.

Results: Patients were grouped according to a cut-off value of 4.825 into the high and low maximum SUV (SUV max) groups using receiver-operating characteristic analysis. Good treatment responses, longer median progression-free survival, and overall survival were observed in the low SUVmax group than in the high SUVmax group. Present of portal vein tumor thrombosis, multiple tumors, high AFP value (>550 g/dl), and high SUVmax were significant predictors of overall and progression-free survival. Similar results were obtained for analyses based on SUV ratios with a cut-off value of 2.355 and on AFP with a cut-off value of 550 g/dl. Double biomarker risk stratification into 3 risk groups using SUVmax and AFP value was identified as a strong prognosticator for predicting survival

outcomes. Significantly less intrahepatic failure in low risk group and more extrahepatic failure in high risk group were observed.

Conclusions: Double biomarker risk groups using SUV and AFP values were strong prognostic factors for treatment outcomes and failure patterns in patients with LA-HCC. It could be a valuable tool to optimize treatment decisions.

0103

Radiotherapy Improves Clinical Outcome in High-Risk Patients of Intrahepatic Cholangiocarcinoma

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Background and Objectives: Treatment strategies for patients with unresectable intrahepatic cholangiocarcinoma (IHCC) have not yet been established, and the overall resectability is difficult to estimate because most studies lack an accurate standard reference for surgery. This study was designed to investigate the role of radiotherapy (RT) in unresectable IHCC.

Methods: Our study cohort comprised 120 patients who were diagnosed with stage I-IVA IHCC between 2001 and 2012. Sixty-four patients received RT as the first treatment with or without chemotherapy, and 56 patients underwent surgery. Locoregional failure-free survival (LRFSS) and overall survival (OS) were compared between patients treated with radiotherapy and with surgery.

Results: The median follow-up time was 36 months (range, 21–136 months). A median dose of 45 Gy (range, 30–60 Gy) was delivered to the primary tumor. Patients who received RT as the initial treatment had more advanced stage tumors (T and N) and multiple tumors as well as more frequent major vessel invasion. LRFSS and OS rates were significantly higher in the surgery group compared to the RT group (3-yr LRFSS: 65% vs. 40%, $p = 0.008$; 3-yr OS: 48% vs. 10%, $p < 0.001$). Multiple tumors, LN metastasis, and major vessel involvement were prognostic factors for LRF in the surgery group by univariate analysis. Those having 2 or more risk factors (multiple tumors, lymph node metastasis, and major vein invasion) were defined as high-risk patients. The median LRFSS of high-risk patients was significantly longer in the RT group ($n = 25$) than in the surgery group ($n = 7$) (15 vs. 3 months, respectively, $p = 0.024$). Eight patients (12.5%) in RT group who were medically inoperable or had unresectable tumors at the time of diagnosis received RT as the first treatment and eventually underwent curative resection.

Conclusions: Although surgery still produces the best outcomes in resectable disease, initial RT could produce better results in high-risk patients. Moreover, RT converted unresectable disease to resectable disease in some patients.

0104

Establishment of Hepatocellular Carcinoma Specific Graded Prognostic Assessment for Patients with Spinal Metastasis

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Background and Objectives: Spinal metastasis (SM) of hepatocellular carcinoma (HCC) is a crucial clinical problem. Stratifying HCC patients with SM might be useful to make individual treatment strategy. However, a specific graded prognostic assessment (GPA) has not been established for HCC patients with SM. In this study, we aimed to develop HCC-SM specific GPA.

Methods: We assessed 192 patients with HCC patients with SM who received radiotherapy from April 1992 to February 2012 at Yonsei University Severance Hospital. After univariate and multivariate analyses, the prognostic factors shown to significantly affect survival were used to build a HCC-SM specific GPA index.

Results: The median overall survival (OS) of all patients was 4.5 months. Using the prognostic factors derived from multivariate analysis, we developed HCC-SM specific GPA index. The relative magnitude of the regression coefficients were used to weight each factor. The weighted factors are as follows; ECOG performance status (2 or below: 0, 3 or above: 1.5), Child-Pugh class (A: 0, B or C: 1), controlled primary HCC (Yes: 0, No:1), visceral metastasis other than bone metastasis (No: 0, Yes: 1), pathologic fracture (No: 0, Yes: 1). The OS rate at 6 months and 1 year were discriminative when applying HCC-SM GPA index: 58.6, 37.2, 12.9, and 9.6% of OS rate at 6 months, 34.2, 15.2, 2.6, and 0% of OS rate at 1 year, for GPA scores of 0 ($n = 64$), 1–1.5 ($n = 62$), 2–3 ($n = 42$), and 3.5 or above ($n = 13$), respectively.

Conclusion: Although the prognosis of patients with HCC patients with SM is poor, the newly developed specific HCC-SM GPA index might be useful to discriminate the prognosis of aforementioned patients. Furthermore, the index can be a valuable tool for selecting patients who might have benefit from active local treatment.

Locoregional Therapy

0006

Usefulness of 4D Ultrasonography to Evaluate Effects Therapeutic Radiofrequency Ablation for Hepatocellular Carcinoma

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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 4D real-time flow imaging 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: 58 patients with 58 HCC lesions (44 men and 14 women, aged 40 to 83 years with a mean age of 61.9 years), admitted to our Masuko Memorial Hospital between November 2007 and February 2011, were enrolled to the present study. Their diagnosis was confirmed by dynamic CT and celiac angiography. Based on Child-Pugh score, 50 patients were diagnosed as grade A, and 8 patients as grade B. All patients enrolled showed hypervascular enhancement of HCC on contrast-enhanced US and/or dynamic CT. 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 VOLUSON730 (GE Medical systems, Milwaukee), APLIO XG (Toshiba Medical Systems) and IU22 (Phillips) for RFA therapy with a convex probe as US system. APLIO and VOLUSON machine probe is mechanical probe and IU22 probe is matrix array probe. 4D Real-time refers here to the display of 3-dimensional moving images composed of 3 orthogonally intersecting scans in the transverse, longitudinal and horizontal planes. RF ablation was carried out under a real-time US guidance. 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 58 HCC patients with 58 nodules using 4D real-time US machines. We confirmed by various angles that the needle was inserted into the center of tumor nodule. The simultaneous study before RFA therapy showed the inflow of arterial blood and tumor stain. And importantly it appeared that 4D real-time US 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 4D real-time ultrasound system. Application of this method allowed a more accurate cauterization of the tumor.

0022

Comparison of Multipolar and Monopolar RFA for Treatment of Hepatocellular Carcinoma

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Background and Objectives: Several types of radiofrequency ablation (RFA) applicator have been applied for treatment of hepatocellular carcinoma (HCC). This study aimed to compare between multipolar RFA (MLT) and monopolar RFA (MON) from therapeutic results and evaluate the appropriate usage as a situation demand.

Methods: Between January 2014 and November 2015, consecutive 140 patients with 247 HCCs treated with laparoscopic RFA, which were diagnosed pathologically or based on typical radiologic findings were enrolled. We retrospectively studied the short-term therapeutic results, ablation time and operation time.

Results: Eighty patients with 137 lesions were treated with MLT and remaining 60 patients with 110 lesions were treated with MON. Median size of main tumor was 21 mm (range, 9–42 mm). MLT treated larger tumors (22.9 mm vs. 19.7 mm, $P < 0.01$). All patients have stayed alive and no major complication encountered during follow-up period. Local tumor progression occurred one case in each treatment group. The 2-year cancer-free survival rates of MLT and MON were 61% and 80%, respectively ($P = 0.25$). The ablation time per nodule of MLT was longer in ≤ 15 mm (10.9 min vs. 8.68 min, $P < 0.01$), no difference in 16–25 mm (16.3 min vs. 16.4 min, $P = 0.95$) and shorter in > 25 mm (24.5 min vs. 39.2 min, $P = 0.02$). The operation time tended to be longer in MLT (147 min vs. 132 min), but there was no statistical significance.

Conclusions: Both of MLT and MON were safe and efficacious procedure for treatment of HCC also with laparoscopic approach. Particularly, MLT was suitable in case with ≥ 25 mm larger tumor. However, MON was considered to be feasible in case with tumor < 20 mm and multiple nodules, because precise insertion of plural applicators took times in MLT.

0024

Survival Prediction Using Prognostic Stratification and Nomogram in Patients Treated with Radiotherapy for Nodal Metastasis from Hepatocellular Carcinoma*Chan Woo Wee¹, Kyubo Kim², Eui Kyu Chie¹, Su Jong Yu³, Yoon Jun Kim³, Jung Hwan Yoon³*

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Background and Objectives: To establish a prognostic model for overall survival prediction in patients treated with radiotherapy for nodal metastasis from hepatocellular carcinoma (HCC).

Methods: One hundred five patients with HCC underwent radiotherapy for nodal metastasis between 2004 and 2015 were accrued for analysis. The median age, biologically effective radiation dose, and follow up period were 60 years, 59 Gy₁₀, and 5.7 months, respectively. Fifty-one patients had nodal metastasis related symptoms.

Results: The median survival (MS) was 5.8 months for all patients. MS for symptomatic patients was 3.8 months compared to 10.7 months for patients without symptom. On multivariate analysis of pre-treatment factors, nodal metastasis related symptoms (HR, 2.93), Child-Pugh class B-C (HR, 2.77), uncontrolled intrahepatic disease (HR, 2.74), and non-nodal distant metastasis (HR, 1.62) were significantly poor prognostic factors for survival. Prognostic grouping into 3 groups by the number of risk factors also had a significant predictive value for survival, with patients having 0, 1, 2, and 3–4 risk factors demonstrating MS of 18.0, 11.7, 5.7, and 3.0 months, respectively ($p < 0.001$). A clinical nomogram based on the 4 prognostic factors was formulated and demonstrated good accuracy for predicting 6-month survival with a concordance index of 0.77.

Conclusions: In a heterogeneous group patients treated with radiotherapy for nodal metastasis from HCC, the presence of related symptoms was highly associated with poor survival. The prognostic grouping and nomogram developed in the current study can be used for the prediction of survival for patients undergoing radiotherapy for nodal metastasis.

0028

Quality Assurance for a Multicenter Phase II Study of Stereotactic Ablative Radiotherapy for Hepatocellular Carcinoma ≤ 5 cm: A Planning Dummy Run*Sun Hyun Bae¹, Mi-Sook Kim², Won Il Jang², Kum Bae Kim², Kwang Hwan Cho¹, Woo Chul Kim³, Chang Yeol Lee³, Eun Seog Kim⁴, Chul Won Choi⁵, A. Ram Chang⁶, Sunmi Jo⁷, Jin-Young Kim⁷*

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Purpose: The Korean Radiation Oncology Group (KROG 12–02) investigated the outcome of stereotactic ablative radiotherapy for hepatocellular carcinoma (HCC) ≤ 5 cm using 60 Gy in 3 fractions. To evaluate dosimetric differences and compliance in a multicenter trial, a planning dummy run procedure was performed.

Methods and Materials: All participating institutions were provided the contours of 2 dummy run cases. Plans were performed following the study protocol to cover the planning target volume (PTV) with a minimum of 90% of the prescription dose and to satisfy the constraints for organs at risk (OARs). We assessed the institutional variations in plans using dose-volume histograms.

Results: Different planning techniques were applied: static intensity-modulated radiotherapy in 2 institutions; CyberKnife in 2 institutions; RapidArc in 2 institutions. The conformity index of all 10 plans was ≤ 1.2 . In terms of the PTV coverage, all participants followed our study protocol. For the second dummy run case, located in segment 8 near the heart, however, the doses covering 99% of the PTVs (D99%) and the maximal point doses of the heart at 0.03 ml (D0.03 ml) were variable because there was no mention of constraints of D99% of the PTV and D0.03 ml of the heart in the study protocol. As an important OAR, the normal liver volumes receiving < 17 Gy in all 10 plans were above 700 ml.

Conclusions: Dosimetric parameters showed acceptable compliance with the study protocol. However, we found the possibility of underdose to the PTV if the HCC lesion was located near OARs. Based on this dummy run, we will conduct individual case reviews to minimize the effects of study protocol deviation.

0031

Impact of Pretreatment Contrast Enhancement Features on Radiotherapy Outcome in Hepatocellular Carcinoma*Jinhong Jung*¹, *Sang Min Yoon*², *So Yeon Kim*³,
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Background: In radiotherapy (RT) for hepatocellular carcinoma (HCC), little is known about pretreatment response prediction. Hypoxia of a tumor makes central necrosis, which is shown as consistent central enhancement defect (CED) in dynamic CT. We hypothesized that CED in pretreatment dynamic CT is a predictive factor of local failure after RT, in HCC. The purpose of this study was 1) to compare outcomes of RT in HCC with or without CED, and 2) to analyze blind reliability test for CED detection.

Methods: We retrospectively reviewed 392 patients who underwent RT for HCC at a single center, from January 2010 to October 2010. Among them, we excluded the patients who were not eligible for the present analysis as follows: 1) patients who had infiltrative HCCs with vascular invasion; 2) patients who received combined therapy with other treatment within 3 months; or 3) follow up (among survivors) periods were less than 2 years. Finally, a total of 202 patients were included. Tumor characteristics on pretreatment dynamic CT, RT dose, and outcomes were measured. With treatment outcomes blinded, presence of CED was decided by 5 physicians' agreements, and inter-observer reliability was tested. With tumor size and RT dose matched, 66 patients with or without CED were assessed by matched-pair analysis. Dose-response relationship was analyzed in both groups.

Results: Median follow up duration was 30.5 months (range 5.6–64.7), and median RT dose (equivalent 2 Gy dose (EQD2)) was 88 Gy (range, 31.3–125 Gy). CED was present in 20.8% of all patients. Local control rate (LCR) and overall survival (OS) were significantly worse in patients with CED (both $p < 0.001$). On multivariate analysis, local recurrence was correlated with tumor size, RT dose, and CED (odds ratios = 4.1, 10.2, 45.5, respectively). In matched-pair analysis, LCR was 26.4% and 79.2%, and OS was 39.4% and 66.7%, in patients with or without CED, respectively, at 2 years (both $p < 0.001$). Inter-observer reliability of CED detection was 89.5% ($p < 0.001$). Hypofractionated RT with EQD2 >70 Gy showed significantly better LCR in both patients with and without CED ($p < 0.001$, $p = 0.039$, respectively).

Conclusions: In patients with HCC, a CED on pretreatment dynamic CT is a potent predictive factor for negative clinical

outcomes, with good inter-observer reliability. To increase treatment outcomes in patients with HCC with CED, high-dose hypofractionated RT or other alternative treatment modalities should be considered.

0036

High Dose and Compartmental Target Volume May Improve Patient Outcome after Radiotherapy for Pelvic Bone Metastases from Hepatocellular Carcinoma*Ik Jae Lee*, *Taehyung Kim*, *Hye Jung Cha*, *Jun Won Kim*,
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Purpose: Pelvic bone metastases are difficult to treat because of complex pelvic bone anatomy and the proximity of normal organs. The adequacy of radiation dose and field coverage was evaluated.

Patients and Methods: We analyzed 146 cases of pelvic bone metastases from HCC treated with radiotherapy (RT). Bone metastases were confirmed using CT/MRI. Subjective pain response was assessed using the visual analogue scale, and treatment-related toxicity with the Common Terminology Criteria for Adverse Events v3.0. Local failure free survival (LFFS) and overall survival were estimated using the Kaplan-Meier method.

Results: The local control rate was 80.1% and the pain control rate was 68.5%. Compartmental target volume (CTV), encompassing the whole compartment of the involved bone, was found to be a significant factor (1-year LFFS, 78% vs. 50%; $p = 0.001$). Sites of metastasis were categorized as either upper or lower pelvic bone; both categories showed improved local control with CTV. In patients showing a partial response, a radiation dose greater than 50 Gy in equivalent dose in 2 Gy fractions (EQD2) was a significant factor for improved local control ($p = 0.009$). No patient showed toxicity higher than Grade IV.

Conclusion: Compartmental RT targeted to the involved bone was associated with improved local control and LFFS. High-dose radiation was associated with an improved treatment response.

0060

Clinical Outcomes of Intraoperative Radiofrequency Ablation in Hepatocellular Carcinoma Patients Ineligible for Percutaneous Radiofrequency Ablation or Surgical Resection

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Objectives: Intraoperative radiofrequency ablation (RFA) is one of the treatment options for hepatocellular carcinoma (HCC) patients with relatively poor liver function to undergo surgical resection or when percutaneous approach for RFA is not feasible due to the difficult location of the tumor. The aim of this study is to investigate the clinical outcomes of intraoperative RFA compared to surgical resection.

Methods: A total of 76 consecutive patients who received either intraoperative RFA (n = 23) or surgical resection (n = 53) with curative intent at the Incheon St Mary's hospital from June 2012 to September 2015 were enrolled. Disease free survival and overall survival rates were analyzed.

Results: The median follow-up period was 20.1 months (range, 0.9–41.5). The mean baseline Model for End-Stage Liver Disease (MELD) score was higher in the RFA group compared to the resection group (11.5 ± 4.7 vs. 7.8 ± 1.5 , $p = 0.001$). The resection group consisted of larger tumors with the median diameter of 2.7 cm (range, 1–16) compared to 2 cm (range, 1–5) of the RFA group ($p = 0.002$). However, there was no difference in the number of tumors and the tumor stage between the two groups. The disease free survival rates at 6 and 12 months were 81.6%, 74.8% in the RFA group and 92.2%, 86.2% in the resection group, respectively ($p = 0.256$). The overall survival rates at one year were 91.3% in the RFA group and 94.3% in the resection group, respectively ($p = 0.635$). In the RFA group, 5 patients (21.7%) received liver transplantation (LT) after median interval of 10.9 months (range, 9.2–26.4) since the intraoperative RFA.

Conclusions: The patients who received intraoperative RFA presented with relatively poor liver function but the disease free survival and overall survival rates were non-inferior compared to the patients who underwent resection. Therefore, intraoperative RFA may be considered as a useful option for patients ineligible to percutaneous RFA and surgical resection, or as a bridge therapy before liver transplantation.

0063

Superior Radiosensitizing Effect of a Novel Drug Lipotecan to Sorafenib with Radiotherapy in Preclinical and Clinical Pilot Studies on Hepatocellular Carcinoma

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Objectives: Obstacles remain for the unsatisfactory response of patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) to radiotherapy (RT), by using either stereotactic body RT or Yttrium-90. Given sorafenib as the only approved drug for advanced HCC, the combination of sorafenib and RT frequently encounters toxicity but not synergistic effect on tumor control. Camptothecin inhibits topoisomerase I, an important enzyme in DNA replication and overexpressed in HCC. Camptothecin is a potential radiosensitizer by preventing DNA repair after RT. Lipotecan, modified by positioning an electron-affinic group around camptothecin structure to enhance the effect, is a potent topoisomerase I inhibitor. Our aim was to investigate whether Lipotecan better sensitizes RT than sorafenib to HCC in preclinical model, and acts as a radiosensitizer in a pilot clinical trial on HCC patients with PVTT.

Methods: Human HCC cell lines (HuH7 and PLC5) were used to evaluate the *in vitro* synergism between Lipotecan or sorafenib and RT. Western blot and immunofluorescence were used to investigate protein expression of DNA repair, whereas annexin-V immunofluorescence was used to measure apoptotic cells after the combined treatment. Severe combined immunodeficient mice bearing intrahepatic HCC xenografts were treated with Lipotecan (40 mg/kg/day x 3 days) or sorafenib (20 mg/kg/day x 9 days) and/or RT (3 Gy/day x 3 days) for the *in vivo* response. A pilot clinical trial recruited HCC patients with PVTT treated with combined Lipotecan (15 mg/m² intravenously for 6 weekly cycles) and RT (50.4 Gy in 28 fractions) for the response of PVTT.

Results: Lipotecan (2.5–37.5 nM) was superior to sorafenib (0.25–3.75 μM) in synergistic cell killing by RT (0–10Gy), in increasing the expression of apoptotic markers, and in suppressing the repair of radiation-induced DNA damages. Lipotecan significantly increased RT-induced death in HCC cells by a mechanism involving the enhanced inhibition of RT-induced DNA-dependent protein kinase catalytic subunit (DNA-PKcs) phosphorylation. In mice bearing orthotopic HCC xenografts, combined Lipotecan/RT significantly improved the tumor-suppressive effect of RT alone by 85.8% and of combined sorafenib/RT by 83.4%, respectively, under the Xenogen *in vivo* imaging system. Three patients receiving combined Lipotecan and RT well tolerated the planned treatments with no adverse effect. Complete response of PVTT was observed in 2 of 3 patients.

Conclusions: Lipotecan is a potent radiosensitizer, superior to sorafenib, with therapeutic value by inhibiting RT activated DNA-PKcs of HCC. The preliminary clinical data encourage the upcoming trial with Lipotecan/RT combination in HCC patients with PVTT.

0065

Stereotactic Body Radiation Therapy for Small Hepatocellular Carcinoma: Long-Term Patient Outcomes

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Objectives: Even with early stage hepatocellular carcinoma (HCC), patients are often ineligible for curative treatments due to advanced cirrhosis, donor shortage, or difficult location of the tumors. Stereotactic body radiation therapy (SBRT) has emerged as an alternative, non-invasive local treatment option for patients with HCC when established curative treatment modalities cannot be applied. In our present study, we report our long-term clinical experiences with SBRT as an alternative treatment for small HCC.

Methods: A total of 292 patients (323 lesions) with HCC who were treated with SBRT were registered between March 2007 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 69.6 months (range, 2.1–220.3 months). The study population was mostly male (79.5%), demonstrating a median age of 61 years. Two-hundred and fifty two (86.3%) patients had liver function of Child-Pugh class A, and median size of tumors was 1.7 cm (range, 0.7–6.0 cm). Only 7 patients (2.4%) 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 3 and 5 years were

63.7% and 44.9%, respectively. Local control rate at 3 and 5 years were 94.0% and 91.8% in all treated lesions, respectively. Intrahepatic recurrence was the main cause of failure and intrahepatic recurrence-free survival rates at 3 and 5 years were 26.4% and 19.0%, respectively. The Child-Pugh class before SBRT had significant effects on overall survival (Child-Pugh A: Hazard ratio = 0.322; 95 CI, 0.219–0.472; $p < 0.001$).

Conclusions: SBRT was an excellent ablative treatment modality for patients with small HCC over a long period of time. SBRT can be a good alternative treatment for patients with small HCCs that are unsuitable for surgical resection or local ablative therapy.

0068

Percutaneous Radiofrequency Ablation versus Repeated Surgical Resection for Recurrent Hepatocellular Carcinoma

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Objectives: The aim of this retrospective study is to compare the clinical efficacy and safety of percutaneous radiofrequency ablation (RFA) and repeated surgical resection (SR) for recurrent hepatocellular carcinoma (HCC).

Method: From January 2002 to November 2014, a total of 100 patients had fewer than three recurrent HCCs, with the largest tumor less than 3 cm in diameter were enrolled in this study. Fifty-seven patients were treated by RFA and 43 patients were treated by repeated SR.

Results: Both groups had comparable baseline data. The overall response rate (98% versus 100%), complication rate (4% versus 7%), and median overall survival time (54 versus 53 months) were not different between RFA and SR groups. RFA group had a shorter hospital stay than SR group (5 versus 13 days, $p < 0.001$). The 1-, 3-, and 5-year overall survival rates were 95%, 63%, and 47% after RFA, and 94%, 73%, and 49% after SR ($p = 0.75$). The 1-, 3-, and 5-year disease-free survival rates were 68%, 42%, and 37% after RFA and 53%, 44%, and 41% after SR ($p = 0.91$). The 1-, 3-, and 5-year re-recurrence rates were 34%, 58%, and 60% after RFA and 47%, 56%, and 59% after SR ($p = 0.79$). The median time to re-recurrence (11 versus 7 months) were similar. Chronic kidney disease, AFP level, histological grade of HCC, and the interval of recurrence

from the initial hepatectomy were significant prognostic factors for overall survival.

Conclusions: Both RFA and SR attained similar survival benefits in the treatment of recurrent HCC. RFA had the advantage over SR in being less invasive, easy to perform and more cost-effective concerning little morbidity and a shorter hospital stay.

0075

A Preliminary Analysis of Stereotactic Body Radiation Therapy With and Without Sorafenib for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Background: To evaluate the efficacy of stereotactic body radiation therapy (SBRT) with and or without sorafenib for advance hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT).

Methods: We retrospectively analyzed 52 HCC patients with PVTT treated with Cyberknife SBRT between January 2009 and December 2014. Of these, Sorafenib was given after SBRT to 16 patients and SBRT alone was given to 35 patients. SBRT was designed to target the liver tumor and tumor thrombosis, radiation dose range from 36–45 Gy (median 40 Gy) in 3–5 fractions.

Results: The mean follow-up for SBRT with sorafenib and SBRT alone were 8.63 ± 7.84 months and 6.57 ± 7.45 months, respectively. At the time of analysis, Response rate was comparable in both groups. CR and PR was 80.8% for SBRT with Sorafenib vs. 74.28% for those without. The median progression-free survival was 6 mo (2–14.5 mos) vs. 3 mo (2–5 mos) ($p = 0.1410$). And the 1- and 2-yrs. progression-free survival rates were 44.8% and 30.8% vs. 13.4% and 10.1% for SBRT with Sorafenib and without Sorafenib group. ($p = 0.0578$). Moreover, there was a trend of benefit for overall survival rate for those with Sorafenib group, the median, 1- and 2-years overall survival rate for SBRT with Sorafenib were 6 (2–14.5) months, 62% and 35.4% respectively. While for those without Sorafenib, the median, 1- and 2-years overall survival rate were 3 (2–6) months, 34.3% and 14.3%, respectively. No patient experienced grade 4/5 toxicity.

Conclusion: The 1- and 2-yrs Progression free survival rate for SBRT with Sorafenib group were of borderline significance. While for overall survival rate, though the median, 1- and 2-yrs OSR were better in SBRT with Sorafenib group. However, the trends did not reach statistical significance. ECOG status, tumor type, PVTT involving the bilateral branch and main trunk were the major factors affecting prognosis in both group. The practical advantage of SBRT with or without

Sorafenib are of particular interest for such poor prognosis patients. Large scale and randomized study is further needed to define the benefit of Sorafenib on SBRT patient.

0084

Effective Downstaging of Large HCC to Resectability with SIRT and TACE

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Hepatocellular carcinoma (HCC) is a leading cause of cancer death in the Philippines and patients usually present in the late stages. Surgery still offers the best chance for cure and it remains a challenge to be able to bring the advanced tumors to a resectable state with neoadjuvant treatment. Selective Internal Radiation Therapy (SIRT) with Yttrium 90 beads is a form of locoregional therapy that has been found to prolong survival in selected patients with intermediate to advanced stage HCC. We present that case of 77-year-old gentleman, diabetic, with cryptogenic cirrhosis who presented with a 16-cm HCC in the right lobe of his liver. His AFP was 2.78 ng/ml. It was abutting the middle hepatic vein and deemed unresectable because the future liver remnant would be inadequate. He was then treated with SIRT and received 1.81 GBq to the tumor via the dominant replaced right hepatic arterial supply. The tumor size decreased to 8 cm. 3 months after the treatment. The medial part of the tumor receiving blood supply from the middle hepatic artery still showed enhancement and was then treated with Transarterial Chemoembolization (TACE) with 40 mg of Doxorubicin and lipiodol. Repeat imaging 2 months later showed further decrease in the size of the tumor to 6 cm. He subsequently underwent partial hepatectomy with wide excision of the tumor. The liver was grossly cirrhotic. He had significant ascites postoperatively but eventually recovered from the surgery. Histopathology showed 98% tumor necrosis with only 2 subcentimeter foci of viable cancer tissue. He remains alive and well, recurrence free 3 years after hepatectomy. This case demonstrates that SIRT in combination with TACE can be an effective strategy to downstage large HCC to allow safe surgical resection and prolong survival.

0092

Carbon-Ion Radiotherapy as a Local Salvage Treatment for Hepatocellular Carcinoma after Transarterial Chemoembolization*Kei Shibuya*^{1,2}, *Hiroyuki Kato*¹, *Shintaro Shiba*^{1,2}, *Daisuke Irie*^{1,2}, *Masahiko Okamoto*^{1,2}, *Hiroki Kiyohara*¹, *Kenichiro Araki*³, *Akira Kakizaki*⁴, *Yoshinori Koyama*⁵, *Tatsuya Ohno*¹, *Ken Shirabe*³, *Takashi Nakano*^{1,2}

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Objectives: Local recurrence of hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) is a serious problem, although TACE is widely performed for unresectable hepatocellular carcinoma that is not suitable for local ablation therapies. Carbon-ion radiotherapy (C-ion RT) has the advantages of its excellent dose distribution and higher biological effect to the radiation-resistant tumors such as hypoxic tumors. The purpose of this study is to evaluate the efficacy and safety of C-ion RT as a local salvage treatment for HCC after TACE.

Methods: From September 2010 to February 2015, a total of 69 consecutive patients with pathologically or clinically diagnosed HCC radically treated by C-ion RT were reviewed. In this retrospective study, we analyzed 25 patients who underwent salvage C-ion RT for recurrent or residual HCC after TACE confirmed by diagnostic imaging. Five patients (20.0%) had two or three lesions in single irradiation field. The median maximum diameter was 3.6 cm (0.9–7.7 cm). Median age was 74 years (range, 37–95). The Child-Pugh classification was A for 20 patients (80.0%) and B for 5 patients (20.0%). The median value of indocyanine green retention rate at 15 minutes was 24.6% (range, 2.4–61.2%). Treatment protocol were 52.8 Gy(RBE) in 4 fractions for 18 patients (72.0%) and 60.0 Gy(RBE) in 4 fractions for 7 patients (18.0%). Primary endpoint was local control rate, and secondary endpoints were overall survival, acute and late adverse events categorized into Grade 3 or more by CTCAE Version 4.0.

Results: The local control rates at 1 and 2 years were 100.0% and 82.1%, respectively. The overall survival rates at 1 and 2 years were 95.8% and 70.5% respectively. During a median follow-up period of 32.3 months (range, 6.7–57.0), no treatment related death occurred. Acute adverse event was not observed. Late adverse events were observed in three patients (8.0%): gamma-glutamyltransferase increased (Grade 3) in one patient and encephalopathy and/or cognitive disability (Grade 3) in one patient. There was no significant difference between Child-Pugh score before and 3 to 6 months after C-ion RT.

Conclusions: C-ion RT demonstrated high local control rate for recurrent or residual HCC after TACE safety. C-ion RT appears to be an effective salvage treatment after TACE.

0105

Radiofrequency Ablation ± Lyso-Thermosensitive Liposomal Doxorubicin (LTLD) in Intermediate-Size Hepatocellular Carcinoma: The Ongoing Phase III OPTIMA Study*Won Young Tak*¹, *Soo Young Park*¹, *Stephen Wong*², *Basri Johan Abdullah*³, *Wattana Sukeepsaisarnjaron*⁴, *Shih-Jer Hsu*⁷, *Craig Pfister*⁵, *Nicholas Borys*⁵, *Shi-Ming Lin*⁶

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Background and Objectives: Radiofrequency ablation (RFA) can safely treat hepatocellular carcinoma (HCC) lesions up to 7 cm maximum diameter (d_{max}), but recurrences are common when d_{max} is >3 cm. Lyso-thermosensitive liposomal doxorubicin (LTLD) consists of the heat-enhanced cytotoxic doxorubicin within a heat-activated liposome. When heated to >40°C, LTLD produces a local doxorubicin tumor concentration up to 25 times that of free (non-liposomal) doxorubicin. We hypothesized that the RFA + LTLD combination could cure 3–7 cm (d_{max}) HCC.

Methods: We tested this premise in the 701-patient HEAT Study (NCT00617981), a double-blind, randomized controlled trial (RCT) of RFA ± LTLD. Study subjects had ≤ four unresectable HCC lesions, at least one of which was ≥3 cm d_{max} and none >7 cm d_{max} . Subjects could be Child-Pugh A or B but were without vascular invasion or extrahepatic disease. The primary endpoint and a key secondary endpoint were progression-free survival (PFS) and overall survival (OS). The study protocol did not require a minimum RFA dwell time.

Results: LTLD is safe, with reversible neutropenia similar to free doxorubicin but without congestive heart failure or hand-foot syndrome. Adding LTLD to the normal practice of RFA did not improve the efficacy of RFA for 3–7 cm d_{max} . When analyzed for LTLD's heat based mechanism, patients treated with RFA for <45 minutes did not benefit from adding LTLD to RFA. However, among the 285 patients with a solitary lesion who received at least 45 minutes RFA dwell time, a subgroup that was balanced at baseline, the overall survival hazard ratio was 0.63 (95% CI: 0.41–0.96, P = 0.04).

Conclusions: Subgroup analysis suggests that LTLD greatly enhances efficacy when RFA dwell time is standardized at ≥ 45 minutes. A computational modeling study and an animal trial both suggest increased efficacy with LTLD when RFA dwell time is ≥ 45 minutes. We are now conducting the OPTIMA Study (NCT02112656), a 550-patient RCT. All subjects will have a solitary HCC lesion 3–7 cm d_{\max} and be Child-Pugh A without vascular invasion or extrahepatic disease. All will receive ≥ 45 minutes RFA; half will also receive 50 mg/m² LTLD and half a dummy infusion. Overall survival is the primary endpoint while progression-free survival and safety are secondary endpoints. If the primary objective is achieved, we will have identified an effective treatment for intermediate-size HCC.

0107

Outcome of Early to Intermediate Hepatocellular Carcinoma Treated with Trans-Arterial Chemoembolization versus Radiofrequency Ablation

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Objectives: Current guidelines for hepatocellular carcinoma recommend the use of RFA for early unresectable tumors and the use of TACE for intermediate unresectable tumours. This may not be possible in many cases either due to technical limitation or patients' choice. Our study goes beyond the guidelines and compares real world clinical outcomes of

early to intermediate HCC treated by TACE or RFA to evaluate TACE as a viable alternative.

Methods: Ours was a retrospective cohort analysis of 248 patients with unresectable hepatocellular carcinoma of BCLC stage A0 to B. Tumor location, technical accessibility for RFA and patients' choice were the main factors affecting the decision for TACE or RFA. Analysis was stratified for size, BCLC stage and nodularity. Outcome measures were complete response, number of treatments required, time to progression and overall survival.

Results: From the cohort, 190 patients underwent TACE, while 58 were treated with RFA. Lesions less than 2 cm required 1.92 (SEM 0.12) locoregional treatments, while those larger than 3 cm required a mean of 2.14 (SEM 0.172). There was no significant difference between TACE and RFA for these sizes. RFA needed significantly fewer treatments for lesions 2–3 cm ($p = 0.041$) with a mean of 1.43 (SEM 0.138) compared to 2.02 (SEM 0.178) for TACE. The chance for complete response was significantly higher for RFA compared to TACE (<3 cm $p = 0.027$ and >3 cm, $p = 0.001$) by Chi-square tests. Even so, there was a significantly longer time to progression for TACE in lesions <3 cm ($p = 0.005$). There was no statistical difference for lesions >3 cm. Finally, no significant difference in survival was noted across all tumor sizes and BCLC classes.

Conclusion: RFA appears to be superior to TACE by providing a significantly better chance for immediate complete response for lesions of all sizes whilst requiring fewer number of treatments for lesions 2–3 cm. However, there is no survival advantage between the two treatment modalities. In addition, time to progression in TACE compared favourably in contrast to RFA in lesions <3 cm. Hence, TACE appears to be a viable alternative to RFA for surgically unresectable early HCC, especially for those not amenable to local ablation.

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