
The 10th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2019)

Novel Evidence and Consensus for HCC Management

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Abstracts

Guest Editors

Norihiro Kokudo, Tokyo

Akinobu Taketomi, Sapporo

Tatsuya Kanto, Tokyo

Nobuyuki Takemura, Tokyo

Masatoshi Kudo, Osaka

Kiyoshi Hasegawa, Tokyo

Ryosuke Tateishi, Tokyo

Hideki Yokoo, Asahikawa

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Contents

Lecture Abstracts

Presidential Lecture (PL)	1
APPLE Presidential Lecture (APL)	2
State-of-the-Art-Lecture 1 (SL1)	3
State-of-the-Art-Lecture 2 (SL2)	4
State-of-the-Art-Lecture 3 (SL3)	5
Technical Tips Session: Technical Tips for HCC Treatment (TTS1-7)	6
Consensus Meeting: How to Improve OS in Intermediate Stage HCC (CM)	13
Symposium 1: HCC Guidelines Worldwide (S1)	14
Symposium 2: Hot Topics in Pathology Diagnosis and Molecular Pathology of HCC (S2)	19
Symposium 3: Optimal Therapy for Small HCC (Resection vs. RFA) (S3)	23
Symposium 4: Hepatitis and HCC – Bringing Basic Science to the Clinic (S4)	28
Symposium 5: Liver Cancer in Asia (S5)	33
Symposium 6: Molecular Targeted Therapy: Regional Difference of Treatment Strategy for Intermediate/Advanced Stage HCC Patients in an Era of Multi-Targeted Agents (S6)	38
Symposium 7: Ablation Therapy for Hepatocellular Carcinoma in Asia (S7)	44
Symposium 8: New Technics for Surgical Treatment (S8)	49
Symposium 9: Immunotherapy (S9)	54
Symposium 10: Cutting Edge of Diagnosis (S10)	59
Symposium 11: Liver Transplantation for Primary Liver Cancer (S11)	66
Symposium 12: Radiotherapy for Hepatocellular Carcinoma (S12)	70
Sponsored Symposium (SS1-3)	74

Special Oral Session Abstracts (SPS-001-005)

82

Oral Session Abstracts

Biomarkers / Cell Biology and Translational Research (O-001-007)	86
Diagnosis and Liver Imaging / Epidemiology and Surveillance / Miscellaneous (O-008-016)	90
Treatment: Surgical Resection and Transplantation (O-017-030)	97
Treatment: Clinical Trials (O-031-035)	104
Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy (O-036-040)	108
Treatment: Systemic, Targeted, Novel Target or Experimental Therapy (O-041-044)	111
Molecular Pathogenesis and Pathology / Staging and Prognosis (O-045-048)	114
Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy (O-049-054)	123
Treatment: Systemic, Targeted, Novel Target or Experimental Therapy (O-055-060)	127
Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy (O-061-064)	131
Treatment: Systemic, Targeted, Novel Target or Experimental Therapy (O-065-069)	133

Poster Session Abstracts

Biomarkers / Cell Biology and Translational Research (P-001-006)	137
Viral Hepatitis / Cirrhosis and Related Complications (P-007-012)	140
Diagnosis and Liver Imaging / Epidemiology and Surveillance / Miscellaneous (P-013-017)	144
Molecular Pathogenesis and Pathology / Staging and Prognosis (P-018-022)	146
Treatment: Systemic, Targeted, Novel Target or Experimental Therapy (P-023-031)	150
Treatment: Surgical Resection and Transplantation (P-032-042)	155
Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy (P-043-053)	161
Biomarkers / Cell Biology and Translational Research (P-054-056)	167
Viral Hepatitis / Cirrhosis and Related Complications (P-057-059)	170

Diagnosis and Liver Imaging / Epidemiology and Surveillance / Miscellaneous (P-060-068)	172
Molecular Pathogenesis and Pathology / Staging and Prognosis (P-069-071)	180
Treatment: Systemic, Targeted, Novel Target or Experimental Therapy (P-072-076)	181
Treatment: Clinical Trials (P-077-078)	183
Treatment: Surgical Resection and Transplantation (P-079-085)	184
Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy (P-086-098)	189
Author Index	199

Lecture Abstracts

Presidential Lecture

PL

What Have Liver Surgeons Achieved in the Recent Decade for the Patients with Liver Cancer?

Norihiro Kokudo

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery,
National Center for Global Health and Medicine, Tokyo, Japan

Thanks to pioneering liver surgeons in the Asian-Pacific region in the past 3 decades, surgical treatment for hepatocellular carcinoma (HCC) including liver resection and liver transplantation has been established and has become a mainstay for curative treatment. If we look back the very recent decade, there have been a substantial evidence created for better outcome of surgical treatment. In my talk, I would like to highlight such major achievements to appreciate our colleague surgeons' devoted works and emphasize the importance of multidisciplinary approach for the future.

Treatment of Small HCC: A SURF trial, a head-to-head randomized controlled trial comparing liver resection and RFA for HCC ≤ 3 cm and ≤ 3 nodules has completed patient accrual and the interim analysis showed similar DFS for both treatments. The two curative treatments may be tailored for each patient with small HCC. **Role of Liver Resection for Vascular Invasion:** There has been a consensus among Asian-Pacific liver surgeons established on the role of liver resection for macrovascular invasion. There has been a number of reports including Japanese national data showing the better OS or DFS for liver resection over other non-surgical treatments in this setting. **Expanded Criteria for Liver Transplantation:** There have been a number of expanded criteria proposed from transplant centers worldwide to save extra-Milan cases with certain conditions. Recently, all-Japan criteria, so-called "5-5-500 criteria" have been proposed based on the Japanese national registry data of LDLT for HCC. These criteria have been promptly accepted by the government policy for deceased donor liver transplantation. **Molecular Target Agents and Immuno Check Point Inhibitors:** The recent development of drug therapy for HCC has been remarkable and there are a number of clinical trials ongoing on adjuvant and neoadjuvant drug therapy in combination of surgical treatments. So far, there has been NO effective adjuvant therapy established after curative surgical treatment. However, with upcoming results of promising on-going trials, MDT team approach will become more and more important for HCC surgical candidates.

APPLE Presidential Lecture

APL

What a Wonderful Journey? Evolution of Systemic Therapy for HCC

Ann-Lii Cheng^{1,2}

¹National Taiwan University Cancer Center, ²National Taiwan University Hospital; Department of Oncology

Looking back, just 13 years ago, there was no any single drug approved for the treatment of advanced HCC. But we have now a total of 7 drugs in this indication. The success of molecular targeted therapy (MTT) and immune checkpoint inhibitor (ICI), and in particular various promising combinations of these agents, has spurred the pursuit of highly efficacious regimens that may hike the tumor response rate to 30–50% and median overall survival to 15–20 months for advanced HCC. However, before these can be mingled into our daily practice, the problems of the accompanied toxicities should be reasonable solved.

When efficacious systemic therapy for HCC is available, it is reasonable to ask whether it can also benefit patients with earlier-stage diseases. Several phase III trials are now testing ICI or ICI-containing combinations in adjuvant setting for high-risk resected/ablated patients. The latter refers to patients who receive surgery or ablation beyond the BCLC boundary, a practice that has already been widely accepted in Asian countries. HCC has now rejoined all other cancer types, for which adjuvant therapy is given primarily to those who have high risk of recurrence after curative treatment.

We have also observed a higher quality of tumor remission in ICI responders. Durable remission is common, and thus residual primary tumors or oligometastases may benefit from further resection or loco-regional therapy. A multi-disciplinary team has become more and more important even in cases with advanced diseases.

In conclusion, systemic therapy for HCC has evolved rapidly from literally nothing to burgeoning prosperity, and is poised to change the treatment paradigm for all stages of diseases.

State-of-the-Art-Lecture 1

SL1

Landscape of Tumor Cell Communities and their Impact on Immunotherapy in Liver Cancer

Xin Wei Wang^{1,2}, Lichun Ma¹, Maria Hernandez^{1,6}, Yongmei Zhao⁶, Sean Martin^{1,3}, David Kleiner^{2,4}, Tim Greten^{2,5}

¹Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, ²Liver Cancer Program, Center for Cancer Research, National Cancer Institute, ³Surgical Oncology Program, Center for Cancer Research, National Cancer Institute, ⁴Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, ⁵Thoracic and GI Malignancies Branch, Center for Cancer Research, National Cancer Institute, ⁶Frederick National Laboratory for Cancer Research

Cancer is the result of an evolutionary process leading to vast intratumor and intertumoral molecular heterogeneity and a complex mutational landscape. Tumor cellular diversity is key factor for therapeutic failures and cancer-related mortality. This is especially relevant to hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), the two major histological types of liver cancer, where various etiological factors may elicit different molecular mechanisms to initiate carcinogenesis, which lead to different molecularly distinct subtypes and complex tumor cell communities. Such heterogeneity poses a major challenge to define drivers responsible for early stage hepatocarcinogenesis and develop diagnostic tools and effective treatment modalities for HCC and iCCA. Characterization of tumor cell communities at the single-cell level may help shed light on the panorama of tumor biodiversity. We determined single-cell transcriptome and cellular landscape of HCC and iCCA from patients who were enrolled for immune checkpoint inhibition trials at the NIH Clinical Center. We found varying degrees of transcriptomic heterogeneity in malignant cells within and between tumors as well as diverse landscapes of tumor microenvironment (TME) by performing t-distributed stochastic neighbor embedding analysis and constructing single-cell trajectory. We found evidence of heterogeneity in cell stemness using liver cancer-related stemness genes. We developed a method to measure intratumoral diversity. Strikingly, intratumoral diversity of malignant cells was associated with patient outcomes where tumors with higher diversity were associated with worse prognosis and TME reprogramming. The link between intratumor heterogeneity and patient prognosis was also observed in bulk genomic and transcriptomic profiles from 765 patients. By searching upstream regulators of diverse landscapes of TME, we found a link between hypoxia-dependent VEGF expression in tumor diversity and TME polarization. Moreover, T cells from higher heterogeneous tumors showed lower cytolytic activities. Our results offer insight into the diverse ecosystem of liver cancer and its impact on TME reprogramming and patient prognosis, and also provide a mechanistic rationale for the ongoing clinical trials of a combination therapy of immune checkpoint inhibitors and anti-vascular treatments.

State-of-the-Art-Lecture 2

SL2

Current Surgical Therapies for Hepatocellular Carcinoma in Japan

Akinobu Taketomi¹

¹Hokkaido University

Although several evidence-based guidelines have been proposed for the treatment of hepatocellular carcinoma (HCC), the criteria and range of indications differ among these guidelines according to the circumstances of each country. In Western countries, patients with the Barcelona Clinic Liver Cancer stage 0-A are only subjects for surgical resection. On the other hand, in Japan, the patients with ≤3 nodules, regardless of tumor size could be considered for hepatic resection. Patients should not be precluded from surgical resection even if portal vein tumor thrombus is present, so that Japanese guidelines recommend the widest surgical indication. Furthermore, the role of living donor liver transplantation, but not deceased donor, in patients with HCC has evolved over the past three decades in Japan. In this lecture, I will present the current surgical therapies for HCC in Japan, and discuss its problem and future perspectives.

State-of-the-Art-Lecture 3

SL3

Improvement in Percutaneous Ablation for Early Stage HCC

*Namiki Izumi*¹

¹Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Japan

Percutaneous ablation therapy for HCC include ethanol injection, microwave coagulation and radiofrequency ablation (RFA). Among them, RFA by twice or three time puncture with two or three ablation for each electrode is the most common procedure carried out in Japan, however, microwave coagulation has been widely used because of improvement of electrode to achieve expanded ablative area up to 5 cm. In Japan, the effects of ablation was usually confirmed by contrast-enhanced CT scan taken one or two days after ablation, and if residual area was detected, ablation with RFA or microwave was again carried out next week until unstained low-density area along the entire complete ablative margin was achieved. It will better to evaluate treatment success using three dimensional construction of contrast-enhanced CT scan before and after RFA, using workstation. In our hospital, we have treated more than 1,000 patients having ≤ 3 nodules each measuring 3 cm by RFA, and 5 year over-all survival after RFA is higher than 70%.

SURF trial was carried out to compare the initial treatment effects between surgical resection and RFA in early stage HCC with numbering 3 or fewer each measuring 3 cm or less. The patients had indications both for surgical resection and RFA determined by joint chart review including surgeons and hepatologists, and they were randomized 1 to 1 ratio to surgical resection and RFA. Total 312 patients were included in the study. Three-year recurrence free survival (RFS) was evaluated by Kaplan-Meier analysis, and RFS was not different between surgical resection. No serious adverse events were not observed both in surgical resection and RFA. This results were reported in ASCO 2019 as an oral presentation. From these data, RFA was recommended as the first line treatment equally with surgical resection for early stage HCC ≤ 3 nodules and ≤ 3 cm, if the HCC nodules are not located near bile duct or gastrointestinal tract.

Technical Tips Session: Technical Tips for HCC Treatment

TTS1

Open Hepatectomy for Advanced Primary Liver Cancer

Nobuyuki Takemura¹, Kyoji Ito¹, Fuminori Mihara¹, Norihiro Kokudo¹

¹Department of Surgery, Hepato-Biliary Pancreatic Surgery Division, National Center for Global Health and Medicine (NCGM)

Hepatectomy for hepatocellular carcinoma is a well-established and widely used procedure, but there are still controversial points in its operation method, procedure, and patient selection. I would like to discuss the following four points this time;

- 1) Three types of the Hilar approaches
- 2) Hepatectomy for hepatic malignancy with vascular invasion
- 3) Hepatectomy for large and/or multiple hepatic tumors
- 4) Hepatectomy for impaired hepatic function

1) There are three types of hepatic hilum approaches to performing anatomical hepatectomy, i.e., portal vein staining (Makuuchi's method), Grissonian approach (Takasaki's method), and division of each portal triad (hilar vessel dissection approach). Procedures of these approaches will be shown with the discussion for its indications. 2) Although the prognosis of the patients suffered from hepatic malignancy with vascular invasion remains poor, surgical resection is the only way having a potential to cure for advanced HCC. Surgical approaches for advanced hepatic malignancy will be discussed. 3) It is sometime difficult to determine surgical procedure and indication for large and/or multiple hepatic tumors. Some cases with large and/or multiple hepatic tumors are shown especially focused on surgical techniques and its indications. 4) In patients with impaired hepatic function, appropriate evaluations of hepatic functional reserve and parenchymal volume of remnant liver are essential to select optimal surgical procedures.

The surgical procedures and its indications mentioned above will be shown and discussed with videos in this session.

TTS2**Roles of Indocyanine Green in Surgical Treatments for Hepatocellular Carcinoma**

Takeaki Ishizawa¹, Akihiko Ichida¹, Nobuhisa Akamatsu¹, Junichi Kaneko¹, Junichi Arita¹, Kiyoshi Hasegawa¹

¹The University of Tokyo

Indocyanine green (ICG) has played a crucial role for assuring safety and efficacy of surgery to treat hepatocellular carcinoma (HCC). Conventionally, preoperative measurement of ICG retention rate at 15 minutes (ICGR15) has been used as an indicator of hepatic functional reserve in patients with HCC, which enables surgeons to determine surgical indication and hepatectomy procedures (Makuuchi's criteria). Briefly, the present criteria permits right hepatectomy or trisectoriectomy when the ICGR15 is <10%, left hepatectomy or sectoriectomy when the ICGR15 is <20%, subsegmentectomy or Couinaud's segmentectomy when the ICGR15 is <30%, limited resection when the ICGR15 is <40%, and enucleation when the ICGR15 is 40% or greater. In our previous series, surgery offered overall survival rates of 56% at 5 years even in HCC patients with portal hypertension under the condition that surgical indication and procedures were determined according to the Makuuchi's criteria.

Recently, ICG has also been used as a fluorogenic agent for intraoperative imaging visualizing the extrahepatic bile ducts, hepatic tumors, and boundaries of hepatic segments. For delineation of the bile duct anatomy, known as fluorescence cholangiography, ICG in bile following preoperative intravenous administration (2.5 mg of ICG) or intraoperative intrabiliary injection (0.025 mg/mL ICG solution) is visualized with a near-infrared camera system. Preoperative intravenous administration of ICG (usually 0.5 mg/kg within 2 weeks before surgery) also enables real-time identification of subcapsular hepatic tumors, because ICG tended to accumulate in cancerous tissues of well- or moderately-differentiated HCC and in non-cancerous hepatic parenchyma surrounding poorly-differentiated HCC. This technique is useful to obtain sufficient surgical margins especially in laparoscopic hepatectomy, in which surgeons cannot palpate hepatic surfaces to detect subcapsular small tumors. For identification of hepatic segmental boundaries, ICG solution (0.005 mg/mL) is injected into the corresponding portal veins under ultrasound guidance (positive staining technique). Segmental boundaries can also be identified through enhancement of ischemic regions by fluorescence imaging following closure of the portal pedicle to be removed and intravenous injection of ICG (2.5 mg; negative staining technique). These techniques enable long-lasting visualization of segmental boundaries throughout the surgical procedures, not only from hepatic surfaces but also from raw surfaces during parenchymal dissection, which offers an advantage over conventional dye-staining technique using indigo-carmin.

TTS3**Percutaneous Ablations for Hepatocellular Carcinoma:
Current Status in Asia-Pacific***Shuichiro Shiina*¹¹Juntendo University

Only 20–30 % of HCC patients are candidates for resection. Furthermore, HCC frequently recurs after resection. Image-guided percutaneous ablations are now considered as standard treatment procedures for small and in some institutions for middle-sized HCC. Radiofrequency ablation (RFA) has been the most widely used. In our study, entire tumor ablation was achieved in 99.4% (5,424/5,457) of treatments. In 1,170 primary HCC patients, 5- and 10-year survival rates were 60.2 % and 27.3 %, respectively (Shiina S, et al. Am J Gastroenterol 2012). New-generation microwave ablation (MWA) has been receiving a great deal of attention because it creates a more predictable ablation zone, a larger ablation volume in a shorter time. Outcomes in over 20-year period clearly show that ablations are curative treatments and enable long-term survival. A strategy to detect recurrence at early stage and repeat minimally invasive treatment is useful for HCC, in which recurrence frequently develops. Various innovations and sophisticated instruments, such as a dedicated US transducer for interventional procedures, US contrast agents, a dedicated procedure bed, and multimodality fusion imaging would further improve outcomes in ablation.

Ablation is, however, highly operator-dependent. Its skills and outcomes are different from operator to operator. Our institution is the highest volume center of ablation in Japan, which obliges us to teach technical aspects of ablation to doctors in other institutions and standardize ablation procedure. We have held training programs: 13 domestic programs with 221 Japanese doctors and 6 international ones with 91 foreign doctors. They are composed of lectures, live demonstrations and case studies. In live demonstrations, RFA and new-generation MWA are performed on 15 cases: cases of newly diagnosed cancer not difficult to ablate, tumors below the diaphragm requiring artificial ascites, in the caudate lobe, adjacent to the heart, a portal vein or hepatic vein, over 5 cm, over five tumors, hepatic metastasis, etc. We demonstrate the importance to have appropriate patient posture, usefulness of our original dedicated probe for interventional procedures and our intervention dedicated operation table, and ways to perform ablation under contrast-enhanced US guidance, and with multimodality fusion imaging. Our training programs seem to be useful to understand the basic concept and learn essential technical tips for ablation.

A sophisticated ablation, which is potentially curative, minimally invasive and easily repeatable for recurrence, would be an alternative to surgery in the treatment of HCC.

TTS4**Technical Tips for Precise Laparoscopic Liver Resection in the Treatment of Hepatocellular Carcinoma***Yuichiro Otsuka¹, Hironori Kaneko¹*¹Toho University Faculty of Medicine

Background: Since 1990's, we have suggested that the laparoscopic liver resection (LLR) can provide favorable outcome with early postoperative recovery in selected patients with liver disease including Hepatocellular carcinoma. Minor LLRs, such as left lateral sectionectomy or partial hepatectomy in antero-lateral region of the liver, have been favorable procedures performed laparoscopically. With accumulation of our experience, advanced procedures, which means hepatectomy in postero-superior region or anatomically oriented resections including Major LLRs, have been utilized.

Surgical Technique and Method: Fundamental technique of LLR, which includes maintenance of operative field, choice and use of instruments, isolation and division of vessels, control of hemostasis, can be learned in Minor LLRs. As well as technical stylization, utilization of perioperative diagnostic modality, such as 3D-CT, Ultrasonography (US) and Indocyanine green near-infrared fluorescence (ICG-NIR) imaging, can help to have decision in disease diagnosis, trocar positioning and way of liver transection. In our concept for division of hepatic hilar vessels in anatomical hepatectomy, individual isolation approach is used for hemi-hepatectomy, and Glissonean pedicle approach is used for resection smaller than hemi-hepatectomy. Positive and negative staining technique for detection of portal inflow territory using ICG-NIR is utilized in anatomical hepatectomy.

Results: Three hundred two patients suffering liver disease received LLR. No severe postoperative morbidity above Clavien-Dindo Grade IIIb, except one patient developed cerebral infarction, was observed. In recent series, one third of cases are anatomical resections including Major LLRs. ICG-NIR can help to perform LLR, especially in cirrhotic liver or post-adhesiolysis. Staining technique could contribute to have precise territory based on hepatic anatomy, even in laparoscopic setting.

Conclusion: We believe that benefits of LLR are not only minimally invasiveness, but also precise performance of surgery.

TTS5

How to Perform Effective Conventional TACE?

Shiro Miyayama¹

¹Fukui-ken Saiseikai Hospital

Transarterial chemoembolization (TACE) is an effective treatment option for inoperable hepatocellular carcinoma (HCC). However, its therapeutic effects are strongly influenced by techniques. It is well known that the therapeutic effects of conventional TACE (cTACE) for small HCCs can be changed according to the catheter positioning. When iodized oil is injected at a distal level of the hepatic artery, some iodized oil flows into the portal veins through the peribiliary plexus and tumor drainage. Iodized oil can block the portal blood flow temporarily, followed by gelatin sponge slurry to completely obstruct the tumor-feeding branch. This leads not only to complete necrosis of the tumor including the well-differentiated tumor portion and microsatellite lesions but also to massive peritumoral necrosis. Furthermore, superselective cTACE can treat not only the tumor but also the tumor drainage area by overflowed iodized oil, where HCC cells spread mainly via the portal system and form intrahepatic satellite lesions. Therefore, this technique is an alternative option for small tumors and may contribute to the prevention of tumor spread via the portal system or control preexisting microsatellite lesions, and may reduce the incidence of locoregional tumor recurrence. On the other hand, cTACE for large HCCs sometimes causes severe complications, such as acute tumor-lysis syndrome and systemic embolization when the whole tumor is embolized in a single cTACE session using a large volume of iodized oil. So, we usually perform 2-3 stepwise cTACE sessions for tumors >7 cm at 3- to 10-week intervals. The total dose of iodized oil in a single session should be limited to ?10 mL. In addition, TACE of extrahepatic collaterals and switching of anticancer agents are other key to control large HCCs. To perform effective TACE, an excellent microcatheter-guidewire system and TACE guidance software using data of cone-beam computed tomography (CT) or conventional CT are also useful and they can improve the therapeutic effects and minimize the adverse effects of TACE. In this presentation, I would like to show our cTACE techniques.

TTS6

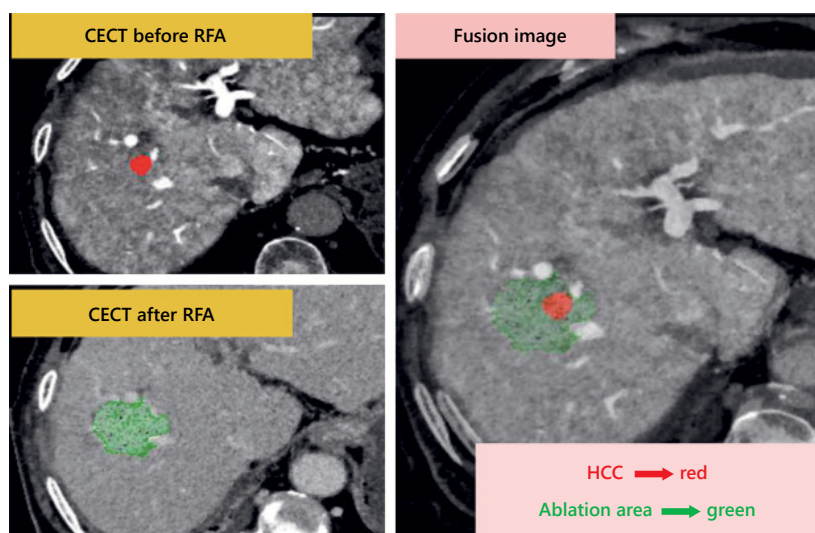
Using Workstation for Diagnosis and Treatment of Hepatocellular Carcinoma*Chikara Ogawa¹, Masatoshi Kudo²*¹Takamatsu Red Cross Hospital, ²Kindai University Faculty of Medicine

The main treatments of hepatocellular carcinoma (HCC) are surgery, loco-regional therapy and systemic therapy. The importance of workstations has been recognized in surgical treatment; it is common during surgery to use workstation for simulation of operations. However it is rarely used in loco-regional therapy and systemic therapy. Recent advances in workstations are remarkable and they have become very useful in treatment. Workstations are highly reproducible and objective, and can be quantified. Today I'll talk about diagnosis and treatment of HCC using a workstation at our hospital.

There are many 3D volume analyzer systems in the world. In my hospital we use workstation SYNAPSE 3D produced by Fujifilm Medical Company in Japan. SYNAPSE 3D is the very famous volume analyzer in Japan and has a lot of useful software for treatment of HCC.

For example, in RFA there is a large dependence on the operator. Using workstation, the disparity become very small. The application, virtual US is useful to understand the relationship of the very small tumor to the surrounding vessels clearly and easily any number of times even if there are no patients nearby. And to evaluate RFA response, we can use one of the useful applications named 2D fusion. Using this application, we can tightly adjust the position of images of CECT before and after RFA to evaluate RFA response, including safety margin. Using these technologies it make it more efficient, safe and reliable to perform RFA.

Another useful applications can be used in TACE and systemic therapy. Collaboration between workstation and experience is important to perform reliable diagnosis and treatment of HCC.

**Fig. 1.**

TTS7

Technical Tips for HCC Treatment

*Kyung-Suk Suh*¹

¹Seoul National University Hospital

The rationale for anatomic resection is based on the assumption that the hepatocellular carcinoma (hcc) invades the nearby portal vein branches and makes daughter nodules. So the anatomic resection means the resection of the tumor-bearing portal territory.

There have been several reports showing the more favorable prognosis in patients underwent anatomic resection than those underwent non-anatomical resection. But still, there are controversies about this procedure.

There are several technical misconceptions in the anatomic resection. For example, in the anterior sectionectomy, some surgeons emphasize that the right hepatic vein and the middle hepatic vein should be fully visualized after resection. However, the concept of the anatomical resection is based on portal tributaries not on hepatic veins. And even smaller resection around the tumor would be done according to the concept of the anatomic resection.

Many patients with hcc have cirrhosis and so larger volume of resection sometimes causes poor prognosis. And rapid regeneration due to large volume of resection may be a risk factor for tumor growth.

Another consideration in HCC resection is the effect of hypoxia, congestion and inflammation of the liver on HCC. Several reports showed the hypoxia, congestion and inflammation are risk factors of tumor recurrence.

With technical advancement of laparoscopic device such as 3 dimensional and flexible scope, the laparoscopically unfavorably located, such as segment 7 and 8, tumors could be laparoscopically resected recently.

In conclusion, in hepatic resection for HCC, anatomic resection is important but also the amount of resection, ischemia and congestion after resection should be considered. And so “functional resection” rather than “anatomical resection” would be the better approach. And the laparoscopic hepatic resection could be done irrespective of tumor location.

Consensus Meeting: How to Improve OS in Intermediate Stage HCC

CM

Changing Paradigm of Treatment Strategy for Intermediate Stage HCC: APPLE Expert Consensus

Masafumi Ikeda¹, Kwang-Hyub Han², Shiro Miyayama³, Hsi-Ming Lin⁴, Su Pin Choo⁵, Yi-Hsiang Huang⁶, Stephen Chan⁷, Masatoshi Kudo⁸, Chung-Kwe Wang⁹

¹National Cancer Hospital East Japan, ²Severance Hospital, Yonsei University, Korea, ³Department of Diagnostic Radiology, Fukui-ken Saiseikai Hospital, Japan, ⁴Chang-Gung Memorial Hospital Linkou, Singapore, ⁵CURIE Oncology, Taiwan, ⁶National Yang-Ming University, Taiwan, ⁷The Chinese University of Hong Kong, Hong Kong, ⁸Kindai University Faculty of Medicine, Japan, ⁹Taipei City Hospital, Ren-ai Branch, Taiwan

The APPLE Expert Panel was organized to develop the APPLE Expert Consensus on emerging treatment strategy for intermediate stage hepatocellular carcinoma (HCC), and the Expert Panel discussed and addressed to critically important clinical questions in daily practice based on published scientific evidence.

Transcatheter arterial chemoembolization (TACE) is the most widely utilized treatment option and is recommended for intermediate stage HCC. However, the tumour burden and liver function status vary among patients with BCLC stage B and TACE is known to be not beneficial in all patients. Recently, multi target agents, such as Lenvatinib, Regorafenib and Ramucirumab, were approved for the treatment of patients with unresectable HCC. Optimal patient selection for treatment within intermediate stage HCC is therefore crucial to improve patients' survival, as choices in real-world settings may not match current international guideline or recommendations.

Objective of this Expert Consensus Meeting was to propose the most up-to-date optimal treatment option in intermediate stage HCC for improving patients' outcome from scientific standpoint of view, and therefore, country specific issues e.g. healthcare insurance, reimbursement policy etc will not be considered. We hope that this Expert Consensus will be able to help clinicians to consider optimal treatment choice for intermediate stage HCC patients. Moreover, we hope that this consensus will eventually contribute to improve treatment outcome for intermediate-stage HCC patients.

Symposium 1: HCC Guidelines Worldwide

S1-1

The Clinical Practice Guidelines for Hepatocellular Carcinoma from the Japan Society of Hepatology

Kiyoshi Hasegawa¹, Takashi Kokudo¹, Nobuhisa Akamatsu¹,
Junichi Kaneko¹, Takeaki Ishizawa¹, Junichi Arita¹

¹The University of Tokyo

There are several guidelines for treatment of hepatocellular carcinoma (HCC) proposed by each region around the world and there are significant differences between each guideline which cannot be explained only by different etiology of HCC. The most varying point would be the management of patients with portal vein invasion. In the AASLD/BCLC guideline, it is considered as an absolute contraindication for liver resection and molecular targeted drugs are the solely recommended treatment. In the EASL guideline, resection can be considered only in prospectively designed protocols. On the other hand, Asian guidelines recommend surgical resection in selected cases. APASL guideline recommend surgical resection for “resectable” cases and HKLC guideline recommend surgical resection if the tumor is not multiple or large. Chinese and Japanese guidelines recommend surgical resection as one of the treatment options. Using the database of liver cancer study group of Japan, we reported that surgical resection was significantly superior to other treatments in HCC patients with macrovascular invasion, therefore it should be at least considered as a treatment option. The current evidence and the guidelines concerning HCC patients with portal vein invasion would be discussed.

S1-2

Hand Foot Skin Reaction (HFSR) Predicts Better Outcomes in HCC Treated with Sorafenib: Analysis of Hong Kong Real-Life Cohort

Thomas Yau¹, Vikki Tang¹, Denise Nie¹, Roland Ching Yu Leung¹,
Gerry Kwok¹, Albert Chi Yan Chan², Kenneth Siu-Ho Chok²,
Simon Tsang², B Li¹, Wong Hoi She², Ka Wing Ma², Joanne Chiu¹,
Tan-To Chueng²

¹Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China; ²Department of Surgery Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China

Background/Aim: Skin toxicity is a known adverse effect of multikinase inhibitors, and was shown to be a predictor of OS in patients (pts) with HCC treated with sorafenib (Reig M, 2014). This retrospective cohort analysis explored whether HFSR with sorafenib was associated with better clinical outcomes.

Methods: Hospital records of consecutive patient with HCC treated with sorafenib in Queen Mary Hospital, Hong Kong from January 2010 to June 2015 were retrieved for analysis.

Results: Of 483 patients with HCC treated with sorafenib (67.7% Child-Pugh A liver function, 75.8% BCLC C tumor and 79.9% HBV), the mOS of the entire cohort was 7.8 months (95% CI: 6.6–8.8). 30.8% (n = 149/483) of patients had onset of HFSR with sorafenib (grade 1: 18.6%, grade 2: 8.1%, grade 3: 4.2%). Duration of treatment, % of subsequent therapy and OS were improved in patients who had HFSR at any time versus those who did not (Table). Dose adjustment/delay and treatment discontinuation due to HFSR were 20.8% (n = 31), and 2.7% (n = 4) respectively. When common prognostics factors, i.e., liver function (Child Pugh class), performance status, tumor burden, HCC etiology (HBV or not), were statistically controlled through multivariate Cox regression analysis, the effect of HFSR remained significant on duration of sorafenib treatment (HR = 0.45, 95% CI: 0.36–0.56, p < 0.001) and OS (HR = 0.44, 95% CI: 0.35–0.55, p < 0.001).

Conclusions: HFSR with sorafenib was associated with longer duration of treatment, more likely to receive subsequently therapy and improved OS in HCC patients. It should be not taken as negative event and discourage treatment maintenance. Active management of HFSR through patient education and dosing adjustment may lead to better outcomes.

Table 1. Outcomes of patients with HCC on sorafenib

Group (n)	mDoT (months), IQR	p-value*	Subsequent therapy, %	p-value*	mOS (months), 95% CI	p-value*
Overall (n = 483)	2.9 (1.2–5.8)	34.8% (n = 168)	7.8 (6.6–8.8)			
HFSR –ve (n = 334)	2.3 (0.9–4.6)	27.8% (n = 93)	5.5 (4.4–6.5)			
HFSR +ve, any grade (n = 149)	5.1 (2.9–10.3)	<0.001	50.3% (n = 75)	<0.001	14.1 (13.0–19.7)	<0.001
HFSR +ve, grade 1 (n = 90)	4.1 (2.6–8.1)	0.001	42.2% (n = 38)	0.010	12.9 (8.9–16.7)	<0.001
HFSR +ve, grade 2/3 (n = 59)	7.1 (3.3–12.5)	<0.001	59.3% (n = 35)	<0.001	21.2 (14.4–27.0)	<0.001

* Versus those without HFSR onset.

IQR, interquartile range; mDoT, median duration of treatment; mOS, median overall survival, CI, confidence interval.

S1-3

Discrepancies between EASL, AASLD and APASL Guidelines

Peter Galle¹

¹Universitätsmedizin Mainz, Germany

Hepatocellular carcinoma (HCC) shows a heterogeneous distribution throughout the world and different guidelines have been developed reflecting expert consensus on the management of HCC in different regions. Since the year 2001 when the European Association for the Study of the Liver (EASL) issued their HCC guideline, at least 20 guidelines have been published or updated thus far, namely guidelines from the American Association for the Study of Liver Diseases (AASLD) for the USA [1, 2], the Asian Pacific Association for the Study of the Liver (APASL) for the Asia-Pacific region [3], the European Association For The Study Of The Liver (EASL) for Europe [4], and the Japan Society of Hepatology (JSH) for Japan [5, 6] and others.

In comparison, the different guidelines regarding the therapeutic management of hepatocellular carcinoma from North America, Europe and Asia-Pacific show clearly visible differences in general concept, but the actual differences in the proposed treatments are limited. The most relevant differences relate to liver resection, as the American Association for the Study of Liver Diseases/European Association for Study of Liver guidelines recommend the presence of a single nodule and a Child-Pugh A functional status, whereas other guidelines accept multinodularity and a Child-Pugh B status, in selected cases [7], an aspect which is also discussed in the West [8].

One important aspect most international guidelines have not yet implemented is the arrival of new kinase (lenvatinib [9] and regorafenib [10]) and checkpoint inhibitors (e.g. nivolumab [11] and pembrolizumab [12]). It can be expected that these drugs will be included in the next updates.

The presentation will provide an updated comparison of the most recent versions of the EASL, AASLD and APASL guidelines.

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S1-4**The Latest Guidelines for Hepatocellular Carcinoma – From a Perspective of Field Practice in the Asian-Pacific Regions***Sadahisa Ogasawara*¹¹Department of Gastroenterology, Chiba University, Graduate School of Medicine, Translational Research and Development Center, Chiba University Hospital, Japan

The extent of tumor burden and liver function significantly affect the prognosis of hepatocellular carcinoma (HCC). The staging system proposed by Okuda et al in 1984 is the first attempt to combine the tumor burden and liver function. Thenceforth, many staging systems for the classification and prognosis of patients with HCC have been proposed. Although numerous validation studies have been reported worldwide, none of these have verified an ideal prognostic staging system considering universal reproducibility in a heterogenous population.

The Barcelona Clinic Liver Cancer (BCLC) staging classification for HCC was first published in 1999. The epoch-making BCLC staging system guides prognostic prediction and treatment allocation of HCC, and it is the first attempt to combine the staging system and treatment algorithm. Although the rigid five staging is inconvenient in field practice, it has become the standard guideline for HCC worldwide. In 2014, the Hong-Kong Liver Cancer Staging System also combined the staging system and treatment algorithm, which was created based on the data of treated patients with HCC in Hong-Kong.

The Asian Pacific Association for the Study of the Liver (APASL) HCC Guideline has been updated in 2017. According to this new guideline, the treatment algorithm is separated from the staging system. Moreover, the use of combined system may be continued due to its universality. Nonetheless, Japan, Korea, Taiwan, and China have their own guidelines. In this session, treatment guidelines will be summarized and discussed from the perspective of the field practice in the Asian-Pacific regions.

S1-5

Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2017 Edition)

Jian Zhou^{1,2,3}

¹Liver Cancer Institute, ²Zhongshan Hospital, ³Fudan University, Shanghai, China

Background: Primary liver cancer, around 90% are hepatocellular carcinoma (HCC), is particularly prevalent in China because of the high prevalence of chronic hepatitis B infection; HCC is the fourth most common malignancy and the third leading cause of tumor-related deaths in China; it poses a significant threat to the life and health of Chinese people.

Summary: Chinese guidelines for diagnosis and treatment of HCC, which were written by more than 60 experts in the field of HCC in China (including liver surgeons, medical oncologists, clinical oncologists, hepatologists, and interventional radiologists), reflect the real-world situation and consensus regarding diagnosing and treating HCC in China.

Key Messages: Most importantly, these guidelines were endorsed and promulgated by the National Health and Family Planning Commission of the People's Republic of China (the counterpart of the Ministry of Public Health) in June 2017.

Symposium 2: Hot Topics in Pathology Diagnosis and Molecular Pathology of HCC

S2-1

Pathology Diagnosis and Subclassification of HCC

Michiie Sakamoto¹

¹Keio University School of Medicine

Outcomes for hepatocellular Carcinoma (HCC) remain poor because the condition is often unresponsive to the available treatments. The number of HCC cases has also been increasing in Europe and the United States in recent years. Therefore, the precise diagnosis of HCC is crucial to achieve improvements in prognosis.

Research on biomarkers associated with malignancy and the biological characteristics of HCC has been done by conventional molecular biological approaches and recent comprehensive genomics and transcriptomics analyses. By analyzing cell signaling features and phenotype immunohistochemically, we proposed a new subclassification of HCC that reflects the degree of malignancy. Additional association with specific pathological subtypes such as scirrhous HCC has been observed and expected to be applied in the clinical practice.

Tumor microenvironment in HCC also seems quite heterogeneous. Vascular stroma changes during progression from early to advanced HCC corresponding to transition from hypo-vascular to hyper-vascular on imaging have been shown. Fibrous stroma is rather rare in HCC, while scirrhous HCC is recognized as a subtype of HCC. It was indicated that steatotic scirrhous HCC has distinct feature from non-steatotic one. Immune cell profile in HCC is also getting more attention due to the rapid progress of immuno-oncology in many types of cancer. Immune hot tumors seem relatively rare in HCC, while they have better prognosis than cold tumor. Interestingly these stromal features seem to have some association with molecular subclass of HCC.

I will discuss these topics in order to understand tumor complexity and heterogeneity of HCC.

S2-2

**Heterogeneity in Tumor Microenvironment of Fibrous
Tumor Stroma and Vasculature in Hepatocellular Carcinoma**Young Nyun Park¹¹Yonsei University College of Medicine

The fibrous tumor stroma and vasculature are important components of tumor microenvironment (TME) of hepatocellular carcinoma (HCC). HCCs usually show no or a little fibrous stroma, whereas HCCs with stemness have a more tendency forming fibrous stroma with aggressive biological behavior compared to those without. The expression of KRT19 in tumor epithelial cells is regulated by cancer associated fibroblast via the HGF-MET-ERK1/2-AP1 and SP1 axis in HCC. Interestingly, the residual HCC after transarterial chemoembolization reveals an increased fibrous stroma and stemness marker expression under hypoxic TME. These features suggest a close cross-talk between cancer associated fibroblast and tumor epithelial cells with stemness. Vascular growth patterns of HCC include capillary and vessels that encapsulate tumor clusters (VETC), which was reported to be linked to HCC metastatic dissemination, recently. We found that VETC >55% of tumor area was associated with high AFP level, poor differentiation and a powerful pathological finding impacting on survival in a large multi-institutional cohort of 541 resected HCCs from Korea, Japan and Italy. It is also enriched in the recently reported macro-trabecular massive HCC subtype which shows a poor clinical outcome. Concerning HCC with atypical imaging feature, irregular rim-like arterial phase enhancement (IRE) has been reported to be associated with more aggressive tumor behavior. We found that IRE-HCCs showed higher proportions fibrous tumor stroma and sinusoid-like microvascular pattern, and higher levels of stemness marker expression compared to non-IRE-HCCs. These features of TME are considered to be involved in IRE of HCC. Taken together, TME including fibrous tumor stroma and vasculature is considered to be heterogeneous and involved in HCC biological behavior.

S2-3

Malic Enzyme 1 is a Potential Marker of Intermediate Cell Carcinoma, a Subtype of Combined Hepatocellular-CholangiocarcinomaHirohisa Yano¹, Yutaro Mihara¹¹Kurume University School of Medicine

Combined hepatocellular-cholangiocarcinoma (CHC) is relatively rare, comprising <1% of all primary liver carcinomas (PLCs). According to the 2010 WHO classification, CHC is classified into classical type and subtypes with stem-cell features including the typical subtype, intermediate-cell subtype, and cholangiolocellular subtype. Transitional features from HCC to intrahepatic cholangiocarcinoma (iCCA) and intermediate features between hepatocellular carcinoma (HCC) and iCCA are often observed in CHC, suggesting that CHCs are derived from hepatic progenitor cells.

According to the most recent paper regarding the terminology for PLC, the CHC subtype with stem-cell features, intermediate-cell subtype was redefined as “intermediate cell carcinoma (INT)”. INT tumor cells show intermediate features in histological features and immunophenotype between HCC and iCCA. Furthermore, INT may be combined with HCC, iCCA, and other stem-cell feature subtypes. Previous studies have revealed that stem-cell features are related to poor prognosis; therefore, accurate identification of the INT component is necessary for its clinical management.

In this study, to identify a specific marker of INT, we examined the gene expression of INT by microarray analysis using formalin-fixed paraffin-embedded (FFPE) samples, and subsequently examined the protein expression of potential key molecules identified in the microarray analysis by immunohistochemistry.

Microarray analysis suggested that malic enzyme 1 (ME1) was significantly upregulated in INT. IHC analysis revealed that the positive rates of ME1 in INT, iCCA, and HCC were 77.1% (27/35), 28.0% (7/25), and 61.7% (37/60), respectively. Analysis of classification and regression trees based on IHC scores indicated that HepPar-1 could be a good candidate for discriminating HCC from the others with high sensitivity (93.3%) and high specificity (96.7%). A multiple logistic regression model and ROC curve analysis based on the IHC scores of ME1, K7, and K19 generated a composite score that can discriminate between INT and iCCA. Using this composite score, INT could be discriminated from iCCA with high sensitivity (88.6%) and high specificity (88.0%).

In conclusions, we propose that ME1 is a useful diagnostic marker of INT when used in combination with other hepatocytic and cholangiocytic markers.

S2-4

Understanding the Complexity and Heterogeneity of HCC

Irene Oi-Lin Ng^{1,2}

¹The University of Hong Kong, ²State Key Laboratory of Liver Research, The University of Hong Kong

HCC is characterized by considerable morphological, molecular and genetic heterogeneity. Morphological classification based on both gross appearance and histology has been widely used clinically for management and prognostication. The new concept of HCC and CC being ends of a disease spectrum will be discussed. Recently, comprehensive genomic analyses using next-generation sequencing technology has revealed the tumor heterogeneity in HCC consisting of inter-tumoral heterogeneity (including that between patients, found in second primary tumors after curative treatment, and synchronous multifocal tumors of different clonalities) and intra-tumoral heterogeneity (within tumors). The information obtained has been very useful in addressing these issues. Several molecular classifications of human HCCs and HCC classification systems using combined histology and molecular findings have been proposed, e.g. a proliferative and non-proliferative phenotype; but they have not been incorporated into clinical practice. It is also to note that the inter-tumoral heterogeneity poses severe challenges for the development and administration of systemic molecular targeted therapies. On the other hand, intra-tumoral heterogeneity has emerged as a characteristic of tumors, with cancer cells within a tumor displaying distinct differences in properties including growth rate, metastatic capacity, and response to treatment. Substantial inter-tumoral and intra-tumoral heterogeneity renders biomarker identification challenging when applied to a single tumor biopsy specimen. As a future perspective, the use of circulating tumor DNA (ctDNA) to evaluate overall tumor heterogeneity may be an option to help resolve this problem. Studying ctDNA could potentially identify more tumor clones and potentially build up a complete picture of tumor heterogeneity in a longitudinal and dynamic manner.

Symposium 3: Optimal Therapy for Small HCC (Resection vs. RFA)

S3-1

Precision Liver Surgery

Jiahong Dong¹

¹Tsinghua University, China

In 2006, We proposed for the first time the novel paradigm ‘Precision Surgery’, featuring multi-objective optimization with certainty-based practice to ensure maximized recovery for each patient. The main characteristics of precision surgery was summarized as determinacy, predictability, controllability, integration, standardization and individualization. Herein, we advocate the practice of precision in liver surgery, which is a complex and ever-challenging surgical arena, to optimize patient recovery with the multiple objectives of therapeutic effectiveness, surgical safety, and minimal invasiveness. The strategy of precision liver surgery is to seek a balance of maximizing the removal of the target lesion, maximizing the functional liver remnant and minimizing surgical invasiveness. We summarized 3 types of liver resection, named positioning liver resection, quantitative liver resection and structured liver resection, respectively. In the paradigm of precision surgery, scientific decision making and surgical planning are crucial and are worthy of further illustration. Technologically, digitized medicine has been playing a key role in improving the ‘predictability’ and ‘controllability’ of surgical practice. A series of novel technologies should be investigated intensively, including 3-D quantitative regional assessment of liver function, intra-operative real-time imaging and navigation, as well as systematic optimization of operative techniques, and digital-assisted decision-making equipment. We believe that precision surgery should be considered for wider application both in liver surgery and in other fields of surgery as a step toward the ultimate goal of perfect surgery.

S3-2

Oncological Efficacy of ALPPS for Early-Staged Hepatocellular Carcinoma

Albert Chi-Yan Chan^{1,2}

¹Queen Mary Hospital, ²The University of Hong Kong, Hong Kong

ALPPS has been advocated for future liver remnant (FLR) augmentation in liver metastasis or non-cirrhotic liver tumors in recent years. Data on the effect of ALPPS in chronic hepatitis or cirrhosis-related early HCC remained scarce. The aim of this study was to evaluate the long-term outcome of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for early-staged hepatitis-related hepatocellular carcinoma (HCC) in comparison with portal vein embolization (PVE). From 2002 to 2018, 148 patients with HCC (hepatitis B: n = 136, 92.0%) underwent FLR modulation (ALPPS, n = 46; PVE: n = 102). Among those who had resections, 65 patients (56.5%) had cirrhosis. ALPPS induced absolute FLR volume increment by 48.8%, or FLR estimated total liver volume ratio by 12.8% over 6 days. When stratified according to tumor stages, the 1-, 3-, and 5-year OS rates for stage I/II for ALPPS (n = 17) were 81.4%, 69.8%, and 58.2%, and the corresponding rates for PVE (n = 43) were 93%, 85.5%, and 74.5%, respectively (P = 0.183). The 1, 3, and 5-year DFS rates for stage I/II for ALPPS were 81.4%, 54.3%, and 40.7%, and the corresponding rates for PVE were 74.3%, 53.8%, and 53.8% (P = 0.664). In conclusion, ALPPS conferred comparable and long-term oncological outcome with PVE for early-staged HCC.

S3-3**Radiofrequency Ablation for Small HCC**Ryosuke Tateishi¹¹The University of Tokyo

Hepatocellular carcinoma (HCC) generally arises with advanced chronic liver diseases or cirrhosis, in which surgical resection is not often indicated. Loco-regional (ablative) therapy was developed more than 30 years ago in Japan as a form of percutaneous ethanol injection to treat unresectable small HCC. Today radiofrequency ablation (RFA) is the *de-facto* standard among loco-regional therapy supported by cumulative evidence including randomized and non-randomized studies. We introduced RFA in 1999; the number of treated cases reached 10,000 in 2016. Because RFA showed higher potency in terms of local tumor control compared to ethanol injection, our interest and effort have been focused on the improvement of accuracy and safety. Artificial pleural effusion facilitates more effective treatment for HCC just under the hepatic dome; artificial ascites provides safe ablation to the lesion adjacent to other organs, especially the intestine. Contrast ultrasonography using the second generation contrast media, Sonazoid[®], facilitates accurate ablation in small HCCs in the coarse liver parenchyma. For small tumors detected with CT or MRI and undetectable with ultrasonography, “fusion-imaging”, a kind of real-time simulation using CT or MRI image as a reference is quite efficient. Although RFA is considered as minimally invasive compared to hepatic resection, patients sometimes encounter various complications, including those potentially critical. We have shown that hemorrhagic complications can be reduced and controlled by careful planning before ablation and immediate procedure to stop bleeding when it occurs. Neoplastic seeding, a late complication that deteriorates long-term survival and has been considered as a major drawback compared to resection, can be reduced by avoiding percutaneous tumor biopsy before ablation and direct puncture to the tumor located on the surface of the liver. Biliary injury, another important late-complication, is still difficult to avoid when the tumor is adjacent to intrahepatic bile ducts. Because patients with HCC have chronic liver diseases with a high risk of recurrence, to find recurrent tumor small in size and maintain liver function is a key to improve long-term survival. With a well-established surveillance system for post ablation and anti-viral treatment for hepatitis B and C, the 10-year survival rate in HCC patients initially treated with RFA in our institution was 29%. The number would be further improved by recently introduced direct-acting antiviral treatments for chronic hepatitis C.

S3-4

No Need of Immediate Treatment for Non-Enhancing Liver Nodules

Yutaka Midorikawa¹, Tadatashi Takayama¹

¹Nihon University School of Medicine, Japan

Early hepatocellular carcinoma (HCC) is usually detected as a hypovascular liver tumor, which can be diagnosed during surveillance for patients at the highest risk for developing HCC, or detected incidentally during imaging studies for patients with classical HCC. However, it remains unknown whether such lesions should be treated immediately or not. Then we focused on the treatment of such hypovascular liver tumor associated with HCC.

After diagnosis of hypovascular tumors smaller than 3 cm in 197 patients, 104 patients underwent liver resection immediately, while 93 patients were placed under observation, and 80 patients underwent liver resection after vascularization or appearance of other hypervascular HCC. The 5-year overall survival rates after surgery of the patients by “immediate resection” was significantly higher than those by “waiting for vascularization” (74.8% vs 59.2%, $P = 0.027$), however, the 5-year overall survival rates after diagnosis were not significantly different between the two groups (75.6% vs 73.2%, $P = 0.591$).

On the other hand, we observed the natural history of non-enhancing and enhancing without washout tumors (defined as “marginal lesions”). In 93 patients who underwent liver resection for classical HCC, there were 138 marginal lesions that were observed without further treatments. In this group, 76 patients had 110 non-enhancing nodules while 17 patients had 28 enhancing without washout nodules. The median interval from resection to the malignant transformation of marginal lesions was significantly longer than that of the appearance of new classical HCC (2.3 vs 1.6 years, $P = 0.002$). Thus, marginal lesions that are coexisting with HCC could be observed, with a new HCC often developing prior to the malignant transformation of these lesions.

Taken together, treatment of hypovascular liver nodules did not significantly improve patient survival outcomes; therefore, patients with such lesions can wait for the development of vascularization or appearance of other hypervascular HCC.

S3-5**Laparoscopic Partial Hepatectomy for Recurrent HCC***Jiwei Huang¹*¹West China Hospital, Sichuan University

Hepatocellular Carcinoma (HCC) is the most common malignant tumour. Liver resection is still the most promising modality for the treatment of HCC. However, the 5-year recurrence rate could reach 80% according to reports. For the resectable lesion after primary hepatectomy, especially via the open approach, abdominal adhesion is usually severe, which is considered not suitable for laparoscopic hepatectomy from traditional point of view. We performed 116 laparoscopic approach partial hepatectomies for recurrent HCC for May 2016–April 2019, the perioperative modality and mobility are not significantly different from the open approach group (n = 124), the during operation blood loss, operative time and postoperative AST/ALT level are not significantly different as well. However, the early recovery activities and the hospital stay is significantly shorter in the laparoscopic group (p = 0.021). Laparoscopic partial hepatectomy for the recurrent HCC is safe and practicable, and it is comparable to open approach resection in perioperative results, but less invasive. Long-term oncological results need further estimation.

Symposium 4: Hepatitis and HCC – Bringing Basic Science to the Clinic

S4-1

Clinical Utility of Biomarkers to Predict HBV-Related HCC

Jia-Horng Kao¹

¹National Taiwan University Hospital

With recent advances in molecular and genomic investigations, the impact of hepatitis B viral and host factors on the progression of chronic HBV infection including the development of hepatocellular carcinoma (HCC) has been explored. For viral factors, hepatitis B viral load (HBV DNA level) is a strong predictor for the risk of HCC. Serum HBsAg level (qHBsAg) serves as a complementary marker to viral load for the prediction of HBV-related HCC in patients with low viral load (HBV DNA <2000 IU/mL). Hepatitis B core-related antigen (HBcrAg) induces host immune responses, and the reduction of HBcrAg level as well as the increment of total anti-HBc level are significantly associated with favorable outcomes. Our recent study indicated that in a long-term follow-up study of 2666 patients with chronic HBV infection (genotypes B or C), level of HBcrAg is an independent risk factor of HCC. Moreover, HBcrAg level of 10 KU/mL could identify patients with an intermediate viral load (HBV DNA 2000–20000 IU/mL) who are at high risk for HCC. In addition, HBV genotypes (genotype C/D) and mutants (basal core promoter and deletion mutation in pre-S genes) are well known viral genetic markers to predict HCC development over time. For host factors, serum inflammatory biomarkers have been developed to evaluate the HBV-associated hepatic necroinflammation and fibrosis. Host single nucleotide polymorphism on sodium taurocholate cotransporting polypeptide (NTCP, an HBV entry receptor) may be associated with a decreased risk for HCC. In conclusion, patients with chronic hepatitis B should be evaluated with relevant viral and host markers to identify those who are at a higher risk of liver disease progression to HCC and then receive timely antiviral therapy.

S4-2

Single Cell Analysis of Tumor-Infiltrating Immune Cells in Liver Cancer

Zemin Zhang¹

¹Peking University

Tumor-infiltrating immune cells possesses special characteristics regarding their types, functional states and cell-cell interactions. We first performed deep single-cell RNA sequencing on thousands of single T cells isolated from peripheral blood, tumor and adjacent normal tissues from hepatocellular carcinoma patients. The transcriptional profiles of these individual cells, coupled with assembled TCR sequences, enabled us to identify T cell subsets based on their molecular and functional properties, and delineate their developmental trajectory. We also outline differences between T cell properties in HCC and those from other cancer indications. We further expanded our single cell analysis to cover a broader collection of CD45+ cells in liver cancer, revealing even more complex patterns of myeloid cell clustering and functional state. We identified a *LAMP3*⁺ dendritic cell cluster which appeared to be the mature form of cDC1 and cDC2. These cells can migrate from tumor to lymph node based on multiple lineage tracing methods, harbor high number of immune regulatory ligands, and are predicted to interact with exhausted or regulatory T cells. In addition, dichotomous macrophages exist in tumor exhibiting differential states and capacity to egress to the ascites. Whereas myeloid cells in ascites were predominantly derived from tumors, tumor-infiltrating proliferative T cells tended to accumulate in ascites. Our data supports a model that immunological dysfunction in HCC tumor microenvironment is partly caused by the differentiation of myeloid cells, thereby serving as a resource for deeper insights into liver cancer progression and potential biomarkers.

S4-3

Novel Immunotherapy Strategies: Cell-Based Immunotherapy in HCC

*Jung-Hwan Yoon*¹

¹Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Synopsis: Hepatocellular carcinoma (HCC) is an aggressive cancer and can recur even when tumors are completely removed. Effective treatments for advanced stage HCC are still lacking. Cell-based immunotherapy is an attractive therapy for HCC with few toxicities. Several strategies including adoptive transfer of autologous activated T lymphocytes, natural killer cells, autologous tumor-pulsed dendritic cells, and cytokine-induced killer (CIK) cells have been tested in human clinical trials. A recent randomized controlled trial demonstrated that adjuvant immunotherapy with CIK cells prolonged both recurrence-free and overall survivals of patients with HCC receiving curative treatment. Moreover, significant gain in recurrence-free and overall survival by adjuvant CIK cell immunotherapy was maintained for over 5 years without boosting. However, tumor response rates are still limited because immunosuppressive factors or cells like myeloid-derived suppressor cells interfere the effects of immunotherapy. The combination of therapeutic regimens that both amplify tumor-specific immunity and counteract these immunosuppressive mechanisms are expected to strongly improve clinical outcomes of cell-based immunotherapy for HCC patients. In addition, we can postulate that it would be more beneficial to combine potent effector cells like CIK cells with immune checkpoint inhibitors (ICIs) because ICIs require eventually effector cells to kill tumor cells.

S4-4

High-Throughput Discovery of Liver Cancer Genes by Forward Genetic Screens

Takahiro Kodama¹, Tetsuo Takehara¹

¹Osaka university, Graduate School of Medicine

Recent advancement of sequencing technology, along with International collaborative efforts, have successfully profiled the genomic abnormality of over 500 hepatocellular carcinoma (HCC) genomes. However, these studies revealed extensive inter-tumor heterogeneity of HCC and the existence of numerous infrequent mutations. In addition, each cancer genome has been shown to have different sets of somatic mutations in 40–80 protein coding genes, suggesting the existence of complex combinations of cancer drivers that contribute to hepatocarcinogenesis. Because of such extreme heterogeneity, it is difficult to generate a comprehensive catalogue of bona fide HCC drivers from human sequence data due to the lack of statistical power. To overcome these difficulties, we have performed several forward genetic screens in mice using transposon mutagenesis and pooled shRNA library, and aimed to discover novel HCC driver genes in a high-throughput manner. First, whole-genome insertional mutagenesis screen was performed using mice harbor liver-specific mobilization of high copy sleeping beauty mutagenic transposons (SBT mice), which identified 1917 HCC candidate cancer genes (CCGs). Then, pooled shRNA libraries targeting 250 selected CCGs were introduced into immortalized liver cells and their tumor-forming ability were monitored. This secondary screen validated 27 new HCC tumor suppressor genes (TSGs). Individual knockdown of four TSGs, including Acaa2, Hbs1l, Ralgapa2 and Ubr2, confirmed their role as anti-proliferative tumor suppressor *in vivo*. Expression levels of all 4 genes were significantly downregulated in human HCCs compared to the non-tumor tissue. We also show that the tumor suppressive function of Ralgapa2 is mediated through Rala and Ralb inhibition, revealing an oncogenic role for the Ral pathway in HCC. Next, another transposon screen was performed to identify non-alcoholic fatty liver disease (NAFLD)-HCC drivers using liver-specific Pten knockout or HFD-fed SBT mice. These 2 screens commonly identified 41 driver genes unique for NAFLD-HCC including Sav1, a component of the Hippo signaling pathway, which was most frequently mutated by SB in both NAFLD models. Liver-specific deletion of Sav1 activated Yap in the Pten knockout mice, leading to acceleration of hepatocarcinogenesis and early death through malignant transformation of liver progenitor cells. Both SAV1 and PTEN mRNA levels were significantly downregulated in non-viral HCC compared to the surrounding liver tissues. Patients with lower expression levels of both SAV1 and PTEN in HCC tissues manifested significantly poorer survival rates than those with higher levels of both. In conclusion, our forward genetic screens successfully identified multiple clinically-relevant novel liver cancer genes.

S4-5

Lipid Metabolic Reprogramming in Hepatocellular Carcinoma

Hayato Nakagawa¹

¹The University of Tokyo

Metabolic reprogramming for adaptation to the local environment has been recognized as a hallmark of cancer. Although alterations in fatty acid (FA) metabolism in cancer cells have received less attention, recent studies have uncovered the importance of lipid metabolic reprogramming in carcinogenesis. Obesity and NASH are well-known risk factors for HCC development, and individuals with these conditions exhibit an increased intake of dietary FAs accompanied by enhanced lipolysis of visceral adipose tissue due to insulin resistance, resulting in enormous exogenous FA supplies to hepatocytes via the portal vein and lymph vessels. This “lipid-rich condition” is highly characteristic of obesity- and NASH-driven HCC. Although how HCC cells adapt to such a condition and exploit it to aid their progression is not understood, we recently obtained new insights into this mechanism through lipid metabolic reprogramming.

We conducted untargeted metabolomics profiling using obesity- and NASH-driven HCC mouse models, and unexpectedly found suppression of fatty acid β -oxidation (FAO) and subsequent extensive accumulation of acylcarnitine species in NASH-driven HCC. These phenomena were caused by downregulation of CPT2, a key enzyme of FAO. CPT2 downregulation enabled HCC cells to escape lipotoxicity by inhibiting Src-mediated JNK activation, and accumulation of acylcarnitine (specifically AC18:1) enhanced carcinogenesis by conferring stem cell properties to HCC through STAT3 activation. Interestingly, in obesity-driven HCC, glucose was utilized for oxidative phosphorylation to compensate suppressed FAO, unlike the Warburg effect. Similar metabolic alterations were confirmed in patients with NASH-related HCC. Altogether, CPT2 downregulation-mediated lipid metabolic reprogramming not only enables HCC cells to escape lipotoxicity but also promotes hepatocarcinogenesis through accumulation of acylcarnitine as an oncometabolite.

In addition, we analyzed the detailed serum acylcarnitine profiles in 241 biopsy-proven NAFLD patients using LC-MS/MS and found that serum acylcarnitine profiles were associated with various aspects of the pathophysiology of NAFLD including inflammation, fibrosis, and HCC. Especially, AC18:1 was significantly positively correlated with serum levels of inflammatory cytokines and significantly increased in NAFLD patients with HCC, which were consistent with mouse experiments. Although none of the acylcarnitine species were independently associated with the presence of HCC, $(AC16:0 + AC18:1)/AC2:0$, an index for the diagnosis of CPT2 deficiency, was independently associated with the presence of HCC after adjusting for age and liver fibrosis stage, likely reflecting the downregulation of CPT2 in HCC tissues. Thus, acylcarnitines merit further investigation for their utility as biomarkers for NAFLD and implications in the pathogenesis of NAFLD.

Symposium 5: Liver Cancer in Asia

S5-1

Liver Cancer in Mongolia

Oidov Baatarkhuu^{1,2}, Jadamba Tsolmon¹, Jazag Amarsanaa²

¹Mongolian National University of Medical Sciences, ²Mongolian Association for the Study of Liver Disease

Viral hepatitis B and C are one of the major causes of liver cirrhosis and liver cancer in Mongolia. 92–95% of HCC patients in Mongolia are related with HCV and HBV co-infections and occurring in 115 cases per 100,000 people per year. However, liver cancer is still one of the serious public health concerns in Mongolia.

Mongolia, where approximately 3.2 million people live, has around 2000–2200 new cases of HCC every year. In last 16 years, cancers have always been in the second place among causes of mortality in Mongolia. According to 2018, national statistics of Mongolia, liver cancer is the most prevalent malignancy which is equal to 44.0% of all cancers in Mongolia. This study population was consisted of 195 subjects from 4 hospitals in UB city of Mongolia and age ranged from 30 to 86 year-olds.

The risk factors associated with HCC development were history of acute hepatitis, chronic hepatitis and the presence of liver cirrhosis. Of these, the presence of liver cirrhosis was the strongest risk factor. The most common etiology for HCC in our patients was HCV infection which is 46%, HBV infection -34%, co-infection B and C -14% and alcohol which is 6.0%. According to the results of our study over 60% of patients had tumor size more than 5 cm. Single tumors was only found in 15%. The mean AFP level was 196 ng/ml. In 18.5% distant metastasis existed. Regarding tumor stage, there was no patient with stage 1. In addition the most patients with HCC were diagnosed in advanced stage. In Mongolia HCC treatment modality is very limited. According to the results of our study, 14% of patients received surgical resection, and their survival was the best. 11.8% of patients received RFA and their survival was 11 months. About 55% of patients received TACE and their median survival was 17 months. The prognosis for patients with supportive care was very poor with a median survival of 5 months. Regarding cause of death, about 50% patients died of HCC progression and the others died of liver failure or GI bleeding. Regarding early detection of HCC in Mongolia, AFP is available in all hospitals except inter-soum and soum's hospitals. Ultrasound is available in all areas. CT, Angiography and TACE are very limitedly available. They can be used at NCC, State Central hospitals and some private clinics in Ulaanbaatar.

S5-2

Epidemiology and Natural History of HCC in Myanmar

Khin Maung Win¹, Aung Hlaing Bwa¹, Soe Thiha Maung¹, Si Thu Sein Win¹

¹Yangon GI and Liver Centre, Yangon, Myanmar

For the diagnosis of HCC, AFP and ultrasound and/or CECT were used. Most of the patients presented with RUQ discomfort/pain and if ultrasound revealed SOL, the diagnosis was confirmed by CECT.

Myanmar has high prevalence of hepatitis B and C carrier rates, 6.51% and 2.65% respectively resulting in the high incidence of HCC. The incidence rates are 25.5 per 100,000 persons per year in males and 8.8 in females.

Regarding the etiology, molecular epidemiology of HCC in YGH jointly conducted by Tokyo National Institute of Infectious Diseases revealed HBV DNA positive in 46.2%, HCV RNA positive in 23.1% and all viral markers negative in 30.8%. Alcohol, NAFLD and Afla-toxin were possible contributors to causation of HCC.

The mean AFP of the patients were 1359 IU/mL with AFP >400 IU/mL in 54% of patients. In CECT, 63% were multifocal lesions and 27% revealed single lesion with non-resectable sizes (>3 cm). The small HCC with resectable SOLs (<3 cm) are seen in only 10% of the patients. 50% of the patients had portal vein invasion at first presentation and 8% of the patients had distant metastases to other organs.

For the early detection of HCC, all the patients with chronic HBV, HCV and other chronic liver diseases should be followed-up with regular ultrasound and/or serum AFP level as the surveillance of HCC.

S5-3

A Current Status of Management in Patients with Hepatocellular Carcinoma in Vietnam

*Thanh Le¹, Quang Nghia Nguyen², Dinh Song Huy Nguyen³,
Cong Duy Long Tran⁴, Cam Phuong Pham⁵*

¹108 Military Central Hospital, ²Vietduc Hospital, ³Bach mai Hospital,
⁴Cho ray Hospital, ⁵University Medical Center HoChiMinh city

Aim: To examine the current status of management in patients with hepatocellular carcinoma in Vietnam from 2010 to 2018, evaluating epidemiological trends of hepatocellular carcinoma (HCC), viral hepatitis B-C in this resource-limited setting and the multiple therapeutic treatment strategies for HCC.

Methods: We extracted data of patients receiving treatment from 6 largest oncology referral centers in Vietnam from 2010 to 2018. We collected information on patient age, gender, geographic distribution, and disease characteristics including disease stage, tumor biomarker levels, and serological testing for hepatitis B virus (HBV), hepatitis C virus (HCV) infections and multiple therapeutic treatment strategies.

Results: According to GLOBOCAN 2018, approximately 94,000 cancer-related deaths, liver cancer accounts for nearly 25,000 in Vietnam. Most patients with hepatocellular carcinoma (HCC) in Vietnam have underlying viral hepatitis, with hepatitis B accounting for about two-third of all the patients and hepatitis C accounting for about 20%. Cirrhosis was found in an estimated 30% to 50% of cases. Over this 9-year period, the incidence of HCC increased, with a large proportion of cases (overall 40%) presenting initially an advanced stage, not amenable to surgical or locoregional therapy.

Conclusion: HCC contributes significant health care burden in Vietnam, with increasing case volume over this nine-year period. HCC remains a huge problem in Vietnam due to virus hepatitis. Despite some improvements in diagnosis and treatment, prognosis of the disease is still very poor. A nationwide screening programme is needed to help detect the cancer early, contributing to improve the prognosis.

S5-4

Combating Cholangiocarcinoma in Southeast Asia

Narong Khuntikeo¹, Watcharin Loilome¹, Attapol Titapun¹,
Paiboon Sithithaworn¹, Nittaya Chamadol¹, Bandit Thinkhamrop¹

¹Khon Kaen University

Cholangiocarcinoma (CCA) is a rare cancer in the western world but very high incidence in the northeast of Thailand and many areas in Southeast Asia. It is aggressive disease leading to a high mortality rate. Liver flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) are the major risk factors. They are classified as group I carcinogenic parasites. To reduce the health burden, a comprehensive prevention and control program for liver fluke and CCA is urgently required.

To date, there is no promising biomarker for diagnosis of CCA. The only tool for screening of CCA is hepatobiliary ultrasonography. This enable the early stage of CCA to be detected, hence, improving results of curative treatment.

A comprehensive approach to tackling these issues being implemented in Thailand under the "Cholangiocarcinoma Screening and Care Program (CASCAP)" is discussed. This program consists of a three-stage prevention and patient care program. The primary prevention component involves liver fluke screening using a new and sensitive essay, followed by praziquantel administration. The second component involves screening for CCA where patients who were suspected CCA defined by either bile duct dilatation or liver mass were referred for confirmatory diagnosis by computed tomography or magnetic resonance imaging (CT/MRI). The tertiary component involves appropriate treatment and end of life care. Due to the eco-epidemiology of opisthorchias-induced cholangiocarcinoma, the anticipated impacts and outcomes of the program include short-, medium-, and the long-term goals for the reduction of the CCA incidence. To achieve the long-term sustainable impacts, concerted efforts to raise social awareness and participating actions by public, non-government organizations and government agencies are necessary. The strategic plans developed for this program can be expanded and implemented in other endemic areas for example the Greater Mekong Subregion (GMS) countries and can be adopted for other chronic diseases.

S5-5

Liver Resection for HCC Beyond BCLC A

Catherine Teh^{1,2,3}

¹National Kidney & Transplant Institute, ²St Luke's Medical Center,

³Makati Medical Center, Philippines

Liver cancer continues to be the 6th most common cancer in the world. In the Philippines, mortality rate is almost equal with the rising incidence rate. It is now the 3rd highest cause of cancer related death. Although surgery is the gold standard in treatment of primary liver cancer, detection and diagnosis is frequently late in low and low middle income countries thus making surgery more challenging. There are different classification systems for the staging for HCC but, not one has been accepted to be used as a world- wide system. The BCLC classification that is based on tumour stage, liver function, physical status and symptoms related to malignancy is one that is used very commonly. Although the BCLC has set an algorithm for treatment based on the clinical factors mentioned above, the role of surgery for tumors beyond BCLC A has not been widely reported. A retrospective analysis on the outcome of all patients with primary liver cancer beyond BCLC A who underwent liver resection at the National Kidney and Transplant Institute from 2010 to 2016 showed 83 out of 196 were beyond BCLC A. Although 96% of these patients fall within Child Pugh A. Majority of the tumors (58%) were more than 10 cms, 17.5% with cirrhosis and portal hypertension. There was no mortality and 5 year survival was at 70%. Hepatic resection for HCC with BCLC staging beyond A has a role that can lead to a long-term survival compared to the current suggested guideline of locoregional therapy. Resection can be performed safely and is associated with low perioperative morbidity and mortality in specialized centers.

Symposium 6: Molecular Targeted Therapy: Regional Difference of Treatment Strategy for Intermediate/Advanced Stage HCC Patients in an Era of Multi-Targeted Agents

S6-1

Molecular Targeted Therapy for advanced HCC: Review of the Clinical Trials Results

Junji Furuse¹

¹Kyorin University Faculty of Medicine

Since it was demonstrated that the efficacy of sorafenib in prolonging the survival of patients with advanced hepatocellular carcinoma (HCC), various treatment agents have been investigated in large phase III trials. In the first-line treatment, lenvatinib, which is a similar multi-kinase inhibitor (MKI) targeting VEGFR, PDGFR and FGFR, was also demonstrated to show non-inferiority to sorafenib in terms of the overall survival in the REFLECT trial. Lenvatinib was approved for the treatment of HCC in 2018 in Japan. Regorafenib, which is a similar MKI to sorafenib, targeting VEGFR, PDGFR and Raf, was shown to provide survival benefit as compared to placebo as the second-line treatment after sorafenib in the RESORCE trial. Regorafenib was also approved in 2017. Furthermore, cabozantinib, a MKI targeting VEGFR and MET, and ramucirumab, an anti-VGFR-2 antibody, were demonstrated to prolong the survival as in second-line treatment agents in the CELESTIAL trial and the REACH-2 trial, respectively. In the near future, therefore, 5 agents would become available for the treatment of advanced HCC.

Intra-hepatic arterial infusion chemotherapy (HAIC) is commonly used for the treatment of advanced HCC in Japan, especially HCC with extensive vascular invasion and/or massive type HCC tumors. However, to date, the survival benefit of HAIC has not been confirmed in a prospective clinical trial. Combination of sorafenib with HAIC using low dose 5-FU and cisplatin failed to demonstrate the prolongation of the overall survival comparing to sorafenib alone in the phase III trial (the SILIUS trial). On the other hand, combined use of sorafenib with HAIC using cisplatin was examined in a randomized phase II trial, and promising results in terms of the overall survival were reported. A phase II trial of combined use of lenvatinib with HAIC is currently under way.

Recent advances in the development of immune checkpoint inhibitors (ICIs) have dramatically changed the cancer treatment paradigms for many cancer types. Various ICIs such as nivolumab and pembrolizumab are under investigation in phase III trials for HCC. The response rate to ICI monotherapy is around 20% and durable duration has been shown in phase II trials. Furthermore, combined use of ICIs with other agents, including molecular-targeted agents or CTLA-4 inhibitors, especially combined use with antiangiogenic agents, including bevacizumab or MKIs, have been demonstrated to yield high response rates of around 40%. As a result, various combination treatments are currently under investigation in phase III trials.

S6-2

Molecular Targeted Therapy: Regional Difference of Treatment Strategy for Patients with Intermediate/Advanced Stage HCC

Joong-Won Park¹

¹National Cancer Center, Korea

The age-standardized mortality and incidence rates of primary liver cancer appear to be declining in South Korea; however, the absolute number of patients associated with primary liver cancer mortality are still increasing. In South Korea, the mortality rate of primary liver cancer is the second highest across all age groups. Hepatocellular carcinoma (HCC) is most common cancer (approximately 85%) of primary liver cancer. Hepatitis B virus (HBV) is the predominant etiology of HCC in Korea and according to several retrospective studies, HBV accounted for 62~75% of HCC.

A substantial proportion of Korean patients with HCC are diagnosed at an advanced stage; more than 35% of patients had Barcelona Clinic Liver Cancer C or D stage tumors at the time of diagnosis. Sorafenib is the standard of care in the management of advanced HCC. Recently, lenvatinib is available for those patients but there is no proven second-line treatment after lenvatinib failure, so it is difficult to use lenvatinib in National Health Insurance System of Korea.

A retrospective observational study based on national health insurance data (2008–2014) showed that the mean duration of sorafenib administration was 106 days and initial sorafenib dose was 600–800 mg in 71% of patients. The most commonly applied treatment after sorafenib failure was TACE but this sequence is changing after availability of regorafenib and nivolumab as a second-line treatment. Recently, a multicenter prospective study showed the median overall survival 10.8 months with sorafenib treatment in patients with far advanced HCC. A multicenter retrospective observational study of regorafenib after progression on sorafenib in Korean patients with HCC reported that the median progression-free survival was 3.7 months and the 1 year OS rate was 54.6%.

2018 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma recommended sorafenib and lenvatinib as a first-line systemic treatment, and regorafenib, nivolumab, cabozantinib and ramucirumab as a second-line systemic treatment for patients with advanced HCC.

In recent phase 3 studies, both nivolumab and pembrolizumab failed to reach the primary objectives, but the acceptable safety profiles of the immunotherapeutic agents warrant the exploration of combination therapy.

The treatment paradigm for patients with unresectable HCC is evolving and it will be important to develop optimal strategies for sequencing or combining systemic agents. The development of predictive biomarkers will be required to inform appropriate stratification of patients.

S6-3

Novelty in Immunotherapy

*Chiun Hsu*¹

¹National Taiwan University Hospital, Taipei, Taiwan

Despite the initial enthusiasm of anti-PD-1 therapy for HCC based on the promising efficacy and safety data demonstrated in single-arm studies (El-Khoueiry AB, et al. Lancet 2017; Zhu AX, et al. Lancet Oncol 2018), randomized trials of anti-PD-1 monotherapy in either first-line (nivolumab vs. sorafenib) or second-line (pembrolizumab vs. placebo) settings failed to meet the primary endpoint of overall survival benefit. Therefore, development of combination strategies has become an even more urgent need to improve treatment efficacy for HCC. In this presentation updated data of clinical trials of combination systemic therapy for HCC will be reviewed. The following issues will be discussed to explore possible novel approaches of immunotherapy for HCC: (1) the balance between efficacy and safety of combination systemic therapy for HCC; (2) perspective of clinical trial design; and (3) exploration of predictive biomarkers.

S6-4**Regional Differences and Changing Treatment Landscape in Systemic Therapy of HCC***Peter Galle¹*¹Universitätsmedizin Mainz, Germany

With the advent of Sorafenib systemic therapy became a treatment option in patients with unresectable HCC. However, in clinical reality the majority of these patients never received systemic therapy and, conversely, even in advanced stage transarterial chemoembolization (TACE) remained a competitor to systemic therapy, despite guideline recommendations. Moreover, impressive regional differences in treatment patterns showed a certain level of arbitrariness.

Over the recent years several TKIs have been approved in addition to sorafenib: lenvatinib in first-line, and regorafenib and cabozantinib in second-line, based on survival advantages in phase III clinical trials. Moreover, the anti-angiogenic antibody ramucirumab has been added to our therapeutic armamentarium. Furthermore, immune-oncological agents are available in some parts of the World, although the data currently are conflicting. Nevertheless, the spectrum of systemic therapy has dramatically evolved over the last ten years and even data, although sparse, for third-line therapy exist.

In view of this extended spectrum of systemic therapy and with the knowledge that TACE may interfere with liver function in a way rendering the patient untreatable with systemic agents, several questions need to be reassessed:

1. In which stage do we use systemic therapy as first option?
2. When do we switch from TACE to systemic therapy?
3. Given multiple options, how do we choose first and second line?

The presentation will cover these points and extend on the ongoing discussion on the general role of systemic therapy in HCC.

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S6-5

Molecular Targeted Therapy: Regional Difference of Treatment Strategy for Intermediate/Advanced stage HCC Patients in a Era of Multi-Targeted Agents Era

*Richard S. Finn*¹

¹Geffen School of Medicine at UCLA, USA

Perhaps, no malignancy has such global variation in our management as HCC. The heterogeneity in our approach influences all stages of the disease including criteria for surgery, techniques in local-regional therapy and when to transition to systemic therapy. While for the past 10 years sorafenib was the only systemic treatment, we now have four positive phase 3 studies with lenvatinib, regorafenib, cabozantinib, and ramucirumab. In addition, both pembrolizumab and nivolumab have accelerated approval for second-line treatment after sorafenib by the US FDA. Now, with so many new therapies available selecting patients for treatment is all that more important to maximize benefit. During the lecture we will review regional differences in practice and how these will change with the increasing number of active drugs in advanced HCC.

S6-6

Rapidly Evolving Strategies for the Treatment of Primary Liver Cancers

Dan G. Duda^{1,2}

¹Massachusetts General Hospital, ²Harvard Medical School

Surgical treatment is a potentially curative treatment option for primary liver cancers such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). However, many of the patients treated with surgery experience disease progression. Moreover, many patients present with unresectable disease at diagnosis. In such cases, until recently, available treatment options have been very limited in efficacy, which led to dismal survival rates. More recent developments in oncology have offered renewed hope for advanced cancer patients. Hypofractionated radiation has shown feasibility and promise in unresectable HCC and ICC setting, and is now being tested in a randomized phase III trial in HCC (clinicaltrials.gov identifier NCT03186898). Antiangiogenic agents have strongly impacted the management of advanced HCC, with multiple drug options in first line setting (sorafenib, lenvatinib) and second line setting (regorafenib, cabozantinib, ramucirumab). Notably, immunotherapy with anti-PD-1/PD-L1 antibodies has shown real potential to transform advanced GI cancer therapy, both in first line and second line settings. Finally, combinations of these new strategies are very attractive approaches, as they promise durable and profound responses in advanced GI cancers. In order to fulfill this promise, these concepts require greater understanding based on mechanistic preclinical studies and validation in correlative studies in clinical trials as a basis to establish optimal combinatorial strategies. I will present results from clinical correlative studies and preclinical models of these diseases performed at our institution. This “bench-to-the bedside and back” approach raises the hope for a more efficient development of targeted agents in advanced setting.

Symposium 7: Ablation Therapy for Hepatocellular Carcinoma in Asia

S7-1

Radiofrequency Ablation in Korea

*Jeong Lee*¹

¹Seoul National University Hospital, Department of Radiology

Radiofrequency ablation (RFA) has emerged as an effective loco-regional treatment modality for malignant hepatic tumors. Indeed, studies have demonstrated that RFA of early stage hepatocellular carcinomas can provide comparable overall survival to surgical resection. However, the incidence of local tumor progression (LTP) after RFA is significantly higher than that of surgical resection. Thus, to overcome this limitation, multiple electrode radiofrequency (RF) systems that use a multi-channel RF generator have been developed, and they demonstrate better efficiency in creating larger ablation zones than that using the conventional RFA with a single electrode. Furthermore, RFA with multiple electrodes can allow the “no-touch” ablation technique which may also help to reduce LTP. Another technique that would be helpful in this regard is multi-modality-ultrasound fusion imaging, which helps to not only more accurately determine the target lesion by enabling the RFA of small, poorly visible or invisible tumors, but also improve the monitoring of procedures and determine the appropriateness of the ablation margin. In addition, new energy sources, including microwave and cryoablation, have been introduced in imaging-guided tumor ablation. In this review, these recently introduced ablation techniques and the results of the most current animal and clinical studies are discussed.

S7-2**RFA in Taiwan***Kaiwen Huang*¹¹National Taiwan University

Interventional treatments are offered to the vast majority of patients with unresectable hepatocellular carcinoma in Taiwan. Radiofrequency (RFA) is among the therapeutic modalities, with the indications which include the presence of up to three lesions, smaller than 3 cm in size, and the absence of extrahepatic disease. The therapeutic effect of the method relies on the thermal injury. Medium-sized hepatocellular carcinoma can be effectively ablated with multiple-electrode switching RFA with comparable mid-term efficacy as smaller medium-sized HCC treated with single-electrode overlapping RFA. Major complications of both methods are comparable and infrequent (approximately 2%-3%), and they include hemorrhage, infection/abscess, visceral organ injury, liver failure, and pneumothorax. RFA may incur the additional complication of skin burns from the electric pad. Nevertheless, there is no compelling evidence for differences in clinical outcomes, including local recurrence rates and survival.

S7-3

Radiofrequency Ablation in Japan

Kazuhiro Nouse¹

¹Okayama City Hospital

Radiofrequency ablation (RFA) is frequently performed for the treatment of hepatocellular carcinoma (HCC) in Japan. According to the latest survey of HCC by the Liver Cancer Study Group of Japan (20th survey), 5249 out of 18458 newly registered HCC patients received local ablation therapy (28.4%) and RFA was used in 89.2% of them. General target for RFA recommended by JSH guidelines is three or fewer lesions, each 3 cm or less in diameter in patients with Child-Pugh A/B. RFA has also been used for the treatment of patients with more advanced HCC. We conducted questionnaire survey in Western Japan (Chugoku-Shikoku district) about RFA procedure consisting of a total of 2113 HCC who received RFA from 27 major hospitals. Surprisingly, RFA was performed for the treatment of BCLC-B HCC in over 70% of the hospitals. The advantage of RFA for the treatment of BCLC-B has been demonstrated by multivariate analysis and propensity score-matched analysis with Japanese cases. In the same questionnaire survey, NAVI system and contrast-enhanced US were routinely used in 59% and 82% of the hospitals, respectively. Both artificial ascites and pleural effusion were adopted in all hospitals but one (96%), and bile duct cooling by endoscopic nasobiliary drainage could be performed in 39% of the hospitals in cases of HCC adjacent to the major branches of bile ducts. The technique of RFA has been matured; however, the skill of each doctor does not seem to be equal. To overcome this problem, periodical training program by experts has been started in Japan.

S7-4

No-Touch Ablation Using Bipolar Electrode in Classical Hypervascular HCC Has the Potential to Prevent Intrasubsegmental RecurrenceYusuke Kawamura¹¹Toranomon Hospital

Background and Aims: The aim of this study was to clarify the utility of a no-touch pincer ablation procedure that uses bipolar electrodes to prevent intra-subsegmental tumor recurrence after RFA for patients with classical hypervascular HCC compared to partial hepatectomy.

Methods: We evaluated 129 consecutive patients with classical hypervascular HCC (single nodule, tumor diameter ≤ 30 mm) who underwent partial resection and 219 patients who received RFA; 184 patients received touch ablation using a monopolar or bipolar RFA device, and 35 received no-touch ablation using a bipolar RFA device. Pretreatment arterial and portal-phase dynamic CT or MRI images were classified into three enhancement patterns: *Type-2* are homogeneous enhancement patterns without or with increased arterial blood flow, respectively; *Type-3* is a heterogeneous enhancement pattern with a septum-like structure; and *Type-4* is an irregularly shaped ring structure enhancement pattern.

Generally, the macroscopic classification of the nodular type of SNEG and CMN types strongly relates to the *Type-3* enhancement pattern, and histologically, the *Type-2* and *-3* patterns represent moderately differentiated HCC; the *Type-4* enhancement pattern is a significantly specific feature for predicting poorly differentiated HCC.

Results: Cumulative recurrence rates significantly differed between procedures (partial hepatectomy, 7.4%; no-touch ablation, 3.0%; and touch ablation, 20.0% at the third year; $P = 0.007$). Multivariate Cox proportional hazards analysis revealed that enhancement pattern type (*Type-3*: hazard ratio [HR], 3.28; $P < 0.001$; and *Type-4*: HR, 4.95, $P < 0.001$), treatment procedure (touch ablation: HR, 3.12; $P < 0.001$), and serum AFP level (≥ 30 $\mu\text{g/L}$: HR, 2.19; $P = 0.002$) were significant predictors of intrasubsegmental recurrence; no significant differences between no-touch ablation and partial resection were observed.

Conclusion: The no-touch ablation procedure using bipolar electrode has the potential to prevent intrasubsegmental recurrence after RFA for patients with classical hypervascular HCC to the same degree as partial hepatectomy.

S7-5

Challenging Precise Ablation: CEUS Guidance & Fusion Imaging Guidance

Yasunori Minami¹, Masatoshi Kudo¹

¹Kindai University Faculty of Medicine

Local ablative therapy has evolved as an alternative to surgical resection for early stage hepatocellular carcinoma (HCC). Radiofrequency ablation (RFA) or microwave ablation (MWA) is an efficient local hyperthermic ablative therapy, and a successful program of percutaneous ablation therapy requires correct targeting via an imaging technique. However, multiple treatment sessions are often required for small HCCs, which are poorly defined on B-mode US. In that difficult situation, it has become more challenging to obtain high local controllability in ablation therapy. Then, we have two approaches in ablation therapy, contrast enhanced US (CEUS) guidance or fusion imaging guidance, for small HCCs with poor conspicuity.

CEUS gains the signal intensity from blood vessels at capillary level through the administration of microbubble contrast agents and can depict tumor vascularity sensitively and accurately. Therefore, CEUS can increase the detectability of small HCCs compared to B-mode US and is very useful for localizing inviable HCCs. Especially, the technique called defect reperfusion imaging makes it possible to depict B-mode ill-defined nodules, locally recurring nodules, nodules found on screening/surveillance, and nodules found during staging. CEUS can facilitate RFA electrode placement in small HCC with poor conspicuity. Either locally recurrent HCCs or new HCCs undetectable on the B-mode US can benefit from CEUS guided ablation therapy. The use of CEUS guidance in ablation therapy for HCC is an efficient approach.

Fusion imaging can provide cross sectional images of volume data on CT/MRI corresponding to the angle of the transducer in the magnetic field. This imaging technique displays a real-time synchronized multiplanar CT/MR image in the same slice of the US plane. Thus, CT/MRI-US fusion image guidance can be useful for placing the therapeutic needle through the center of HCC nodule, especially for nodules demonstrated on CT/MRI, but not on US. Fusion imaging guided ablation therapy is an efficient treatment of patients with HCC that is ill-defined on B-mode US. Recently, the advances of fusion imaging have made it possible to visualize the ablative margin on US. By an overlay of preoperative and postoperative US, the tumor image could be projected onto the white ablation zone in real-time. Therefore, US-US overlay fusion can show the ablative margin during the procedure and be proposed as a feasible guidance method in RFA therapy with a safety margin.

Symposium 8: New Technics for Surgical Treatment

S8-1

Laparoscopic Anatomical Liver Resection with a Novel Positive Staining Technique Using ICG Fluorescent Imaging

Takeshi Aoki¹, Masahiko Murakami¹, Akira Fujimori¹, Tomotake Koizumi¹, Tomokazu Kusano¹, Kazuhiro Matsuda¹, Koji Nogaki¹, Yusuke Wada¹, Tomoki Hakozaiki¹, Kodai Hakozaiki¹, Takahito Hirai¹

¹Showa University

Aim: The technique of anatomic liver resection for hepatocellular carcinoma was published by Makuuchi in 1985 and then demonstrated significant improvements in overall survival and disease free survival. Recently, all segments of the liver can be resected laparoscopically by appropriately trained surgeons with experience in hepatobiliary and laparoscopic surgery. Indocyanine green (ICG) fluorescence imaging are emerging as major contributions to intraoperative decision making during liver surgery. ICG image guidance may be of more importance in minimally invasive anatomic segmentectomy due to the ease of maintaining the segmentation mapping under fluorescence guidance.

Methods: Twenty-one cases laparoscopic anatomical liver resections with the positive staining approach were performed at Showa University hospital between 2017 from 2019. Three methods administering the ICG for positive staining were conducted as follows. A. Preoperative positive staining under US-B mode (Pre-PS): The approach involves using ultrasound to guide the injection of ICG through a long 20-gauge PTCD needle into the portal vein segment immediately before the operation. B. Intraoperative positive staining under intraoperative US (Intra-PS): A laparoscopic ultrasound probe was used to guide the percutaneous freehand injection of ICG with laparoscopic visualization. C. Combination of preoperative and intraoperative positive staining (Combination). In all of these positive staining techniques, 0.025 mg/ml ICG was administered.

Results: Among 52 cases of anatomical liver resections, 21 cases were performed laparoscopic anatomical liver resections with positive staining using ICG fluorescent (Pre-PS: 15 cases, Intra-PS: 4 cases, Combination: 2 cases). 2 cases of Pre-PS were failed staining because of technical failure, but the other cases were successful to stain. With use of positive staining, the target segment exhibit fluorescence within five minute and parenchymal transection proceed guided by fluorescence. Pre-PS staining method was easy and convenient for identification of demarcation line and determination of intersegmental plane. Intra-PS and Combination methods for positive staining allow surgeons to adjust staining area intraoperatively by injecting into other liver segments, clearly identify the intersegmental plane. The median surgery duration, operative blood loss in laparoscopic anatomical liver resection with ICG fluorescent imaging were 235 (range, 55–485) min, 95 (range, 0–535) g, respectively. According to the Clavien-Dindo classification, there were one grade I, four grade II complication. The median hospital stay was 10.5 (range, 6–22) days.

Conclusion: ICG fluorescence positive staining enables surgeons to clearly identify not only segmentation mapping but also intersegmental planes during laparoscopic liver resection, thus enhancing the accuracy of pure laparoscopic anatomic liver resection.

S8-2

New Technics for Surgical Treatment-ICG Guided Navigation Surgery

*Etsuro Hatano*¹

¹Hyogo College of Medicine

Liver resection is the mainstay curative treatment for liver tumors. However, even experienced surgeons face great risk in hepatectomy. In fact, Japanese national clinical database system showed that total mortality is 4%. To perform liver surgery safely, it is essential to control bleeding and to preserve remnant liver function. As surgeons cannot completely view the intra-parenchymal structure, only the hepatic veins are available as landmarks to perform liver parenchymal dissection in many cases. Although 3D simulated imaging of the liver, based on preoperative CT images, has progressed over the years, the liver can move freely and change its shape during surgery, making precise identification of the internal anatomy of the tumor sites or vessels difficult based on static images. More recently, 3D printing has been used to create a see-through model of the liver, which can be used as a reference within the operative field. However, this static approach still does not account for intraoperative movement or deformation of the liver. Therefore, we developed a new imaging device, the Medical Imaging Projection System (MIPS), which uses the indocyanine green (ICG) emission signal and active projection mapping, for liver resection. This system can provide the well-lighted operation field without the astral lamp. MIPS enabled us to project fluorescence imaging, which is acquired by intravenous injection of ICG, onto the actual liver surface. The demarcation lines of the resecting liver was sharply projected after clamping the blood inflow, even if it was difficult to recognize the lines with the naked eyes. Using the new projector, regions preserving the blood flow are immediately and clearly visible in bright light, with the marked areas shifting dynamically as the operation progresses. MIPS clearly showed the demarcation line and the cutting line between the resected and remnant livers, resulting in real-time and continuous navigation for parenchymal dissection of the liver. Our retrospective analysis provides evidence of the feasibility and clinical utility of the MIPS to identify anatomical landmarks for parenchymal dissection. The MIPS holds promise as a novel real-time navigation system for liver resection. The key words of navigation surgery are continuous, color-coded, and comfortable.

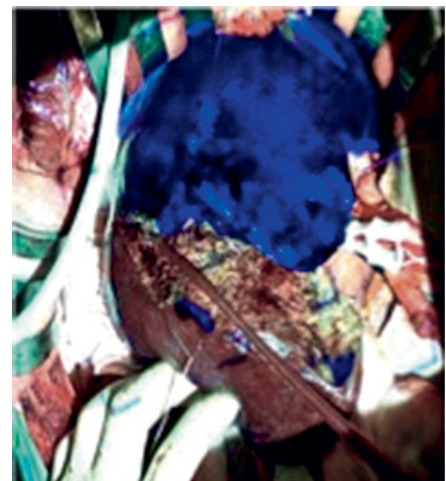


Fig. 1.

S8-3

Robotic Hepatectomy for HCC

Chung Ngai Tang¹

¹Pamela Youde Nethersole Eastern Hospital

Previous studies have demonstrated the safety and feasibility of laparoscopy for minor hepatectomy and now laparoscopy is considered a standard approach. Comparative studies have suggested that laparoscopy is associated with less bleeding, fewer complications, and a better subsequent quality of life than open hepatectomy. However, there are still a lot of limitations of conventional laparoscopic hepatectomy, such as tumor location, tumor size and extent of liver resection. The recent introduction of robotic surgical systems has revolutionized the field of minimally invasive surgery. It was developed to overcome the disadvantages of conventional laparoscopic surgery. Robotic surgical systems can enhance a surgeon's dexterity in the surgical field through a magnified 3-dimensional view, instruments with seven degrees of freedom, and intuitive hand-control movements. The robotic devices can also shorten the learning curve of difficult laparoscopic procedures for inexperienced laparoscopic surgeons and enable expertise to conduct more complex laparoscopic procedures easily.

The principle of hepatectomy for HCC is largely similar to laparoscopic approach which includes anatomical resection with clear margin, caudal-cranial approach, inflow control either glissonian approach or individual ligation, parenchymal resection under "adjusted" pneumoperitoneum and outflow control is mainly with the use of stapling devices. Two new inventions of the da Vinci Xi are "smart" stapler and Firefly technology using ICG. The staple can be adjusted to whatever angles for better alignment of transected tissue and the "smart" stapling technology could eliminate the "bursting" of staple line as firing is not possible without complete (100%) clamping. The use of ICG is not only for better intraoperative localization of hepatoma but also allow surgeons to have better appreciation of segmental anatomy. There are different ways to transect liver parenchyma including ultrasonic dissector, bipolar diathermy or even CUSA controlled by the bedside surgeon. It is often criticized that there are less instrumentations for parenchymal transection as compared to open or laparoscopic hepatectomy but it could be well compensated by the close collaboration between the console and bedside surgeons and that also ensure the safe performance of the procedure.

Although there is still concern regarding cost-effectiveness of the robotic approach and limited available survival data, further technological innovations and industry competition will expectedly lead to greater adoption and acceptance.

S8-4

Laparoscopic Anatomical Segmentectomy with ICG Fluorescence Staining by Aparoscopic Ultrasound and 3D Simulation Guided Portal Branch Puncture Approach

Xiaoying Wang¹

¹Department of Liver Surgery Zhongshan Hospital, Fudan University, China

Objectives: Anatomical hepatic resection could improve survival and limit complications from hepatectomy in hepatocellular carcinoma. The segment identification techniques commonly used in open surgery are blue dye staining and Glissonean pedicle approach. However, Blue dye needs temporarily clamp the hepatic artery and washouts quickly and is unclear under laparoscopic view. Glissonean approach is technically difficult for posterior and superior segmentectomy. Both techniques are impossible to identify the intersegmental plane during division of the liver parenchyma. ICG fluorescence provides clear demarcation lines on both the surface and the deep part of liver. So it is helpful to identify the intersegmental plane during division of the liver parenchyma. Herein, we developed laparoscopic ultrasound and 3D simulation guided portal branch puncture technique to injection ICG to the visualization of segments during laparoscopic anatomical segmentectomy.

Methods: Preoperative 3D reconstruction of the tumor and vessels, and simulation of the perfusion area of portal branches were performed. The portal branches of segments were identified by laparoscopic ultrasound and punctured with the 22-gauge PTCD needle through the abdominal wall under laparoscopic US guide. 5ml ICG dye (0.0125mg/ml) was injected into portal branches without clamping inflow. The target segments started to fluoresce immediately. Liver parenchyma was transected along the fluorescence boundary with Harmonic and CUSA under real-time fusion ICG-fluorescence imaging.

Results: laparoscopic ultrasound and 3D simulation guided portal branch puncture technique was successfully performed in S8, S7, S6, S5, S3 and S2. The intersegmental plane could be identified clearly during division of the liver parenchyma. The hepatic vein and the origin of the Glissonean pedicles of segments were present on the border of fluorescence. However, puncture is difficult in multiple or thin portal vein branches. So, Glissonean approach and negative staining have more satisfaction rate for S1 and S4.

Conclusions: ICG fluorescence staining by laparoscopic ultrasound and 3D simulation guided portal branch puncture technique has great value in laparoscopic anatomical segmentectomy and subsegmentectomy, most appropriate for posterosuperior segmentectomy. This novel technique enables us to clearly identify segments prior to and during parenchymal transection. So, This technique enhance the accuracy of laparoscopic anatomical segmentectomy.

S8-5

Laparoscopic Parenchymal Sparing Anatomical Liver Resection for Liver CancerGo Wakabayashi¹¹Ageo Central General Hospital

To describe laparoscopic anatomical parenchymal sparing liver resections for hepatocellular carcinoma (HCC) and colorectal liver metastases (CRLM) and report the short-term outcomes.

Anatomical resections (AR) have been shown to improve the oncological outcomes in patients with HCC and some suggest should be performed also for CRLM as micrometastasis occurs through the intrahepatic structures. Furthermore, remnant liver ischemia after partial resections has been associated with worse oncological outcomes. Few experiences on laparoscopic anatomical resections have been reported and no data on limited AR exist.

We performed a retrospective analysis of 86 patients undergoing full laparoscopic anatomical parenchymal sparing resections with preoperative surgical simulation and standardized procedures.

Fifty-five patients had HCC while 31 had CRLM with a median of 1 lesion and a size of 30 mm. During preoperative 3D simulation, a median resection volume of 120 ml was planned. Sixteen anatomical subsegmentectomies, 56 segmentectomies, and 14 sectionectomies were performed. Concordance between preoperative 3D simulation and intraoperative resection was 98.7%. Two patients were converted, and 7 patients experienced complications. Subsegmentectomies had comparable blood loss (166 ml, $p = 0.59$) but longer operative time (426 min, $p = 0.01$) than segmentectomies (blood loss 222 ml; operative time 355 min) and sectionectomies (blood loss 120 ml; operative time 295 min). R0 resection and margin width remained comparable among groups.

A precise preoperative planning and a standardized surgical technique allow pursuing the oncological quality of AR enhancing the safety of the parenchyma sparing principle, eventually reducing surgical stress through a laparoscopic approach.

Symposium 9: Immunotherapy

S9-1

Immunotherapy for Patients with Hapatocellular Carcinoma

Yutaka Kawakami^{1,2}

¹International University of Health and Welfare, ²Keio University

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

The response to immunotherapies depends on immune status of patients particularly in tumor microenvironment (TME), which is defined by cancer cell genetic characteristics (e.g. immunogenic DNA mutations, immunosuppressive oncogenes and aneuploidy), patients' genetic immune-reactivity (e.g. immune related gene SNPs, HLA types), and environmental factors (e.g. intestinal microbiota, smoking, UV, diet/obesity, stress). In general, for the patients with cancer cells having sufficient immunogenic antigens such as neo-antigens derived from DNA mutations, ICI based combination immunotherapies using appropriate drugs for the particular subtypes along with PD-1/PD-L1 Ab may be effective. For the patients without immunogenic antigens, gene engineered T cells (e.g. chimeric antigen receptor (CAR-T) or T cell receptor (TCR) gene transduced T cells) may be useful. Therefore, in addition to various ICI based combination immunotherapies, we have been developing T cell based ACTs including tumor infiltrating T lymphocyte (TIL) therapy for metastatic melanoma and chemo-resistant cervical cancer, and CAR-T or TCR-T therapies for various solid cancers including hepatocellular carcinoma (HCC).

For HCC patients, PD-1 Ab monotherapy has been approved in the US, and combination immunotherapies such as PD-1/PD-L1 Abs plus anti-VEGF Ab or VEGF-R inhibitors are currently being evaluated. Transcriptome analyses of HCC tumor tissues define immunological subtypes and suggested that some of the patients with either viral or non-viral HCCs are T cell inflamed (relatively significant CD8+ T cell responses) and may respond to PD-1/PD-L1 Ab monotherapies, but others are T cell non-inflamed and may not respond to PD-1/PD-L1 inhibitors. The T cell non-inflamed HCCs include b-catenin signal activated subtype which may be treated with modulators of b-catenin related molecules and cells, and stem cell like subtype in which cancer cells express high amount of cell surface glypican-3 (GPC3). We have developed CAR-T targeting to GPC3 and GPC1 which are expressed in the subtypes of HCC, and may be useful for the patients with ICI resistant HCC subtypes. Therefore, various immunotherapies may be useful for patients with particular subtypes.

S9-2

Molecularly Targeted Therapy for Intermediate/Advanced Stage HCC Patients – Asian Perspectives

Chih-Hung Hsu^{1,2,3}

¹Graduate Institute of Oncology, National Taiwan University College of Medicine, ²Department of Medical Oncology, National Taiwan University Cancer Center, ³Department of Oncology, National Taiwan University Hospital

Antiangiogenic targeted therapy has revolutionized the care of patients with advanced hepatocellular carcinoma (HCC) and those with intermediate-stage disease not amenable to loco-regional therapies since 2007. As of now, 4 multikinase inhibitors and 1 monoclonal antibody have been approved for the treatment of HCC. Although all the approved targeted agents of HCC are potent inhibitors of vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR), their profiles of target inhibition vary. It is currently unclear how significant the different target inhibition profiles may contribute to the antitumor effect of these targeted agents against HCC. It is also unknown whether the different target inhibition profiles and potential mechanisms of action of these approved agents can be applied to treat patients with HCC tailored to different etiological factors, disease courses, or practice patterns.

Recently, a joint effort of European Society of Medical Oncology (ESMO) and 8 Asian Medical Oncology Societies have been conducted to discuss the Asian perspectives on the “ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with HCC”, published in 2018 (*Vogel A, et al. Ann Oncol 2018; 29: iv238-iv255*). Asian experts agreed with the recommendation of sorafenib and lenvatinib as first-line systemic therapy for patients with advanced HCC and those with intermediate-stage HCC that is not eligible for loco-regional therapies, the recommendation of regorafenib, cabozantinib, and ramucirumab as post-first-line treatment options for HCC, and the recommendation against the routine combination of systemic therapy such as sorafenib with locoregional therapy for intermediate-stage HCC. Many Asian experts, however, emphasized the potential role of systemic chemotherapy in selected patients with advanced HCC. Further, most Asian experts believed that a multidisciplinary approach, involving not only molecularly targeted therapy but also other systemic therapy and locoregional treatment modalities, is crucial for further improving the outcomes of patients with advanced HCC.

S9-3

The Current Clinical Development of and Future Challenges in Utilizing Immune Checkpoint Inhibitors

Shigehisa Kitano¹

¹National Cancer Center Hospital, Tokyo, Japan

Immune checkpoint inhibitors are the most striking innovation in the clinical development of immunotherapy. The first-in-class approved immune checkpoint inhibitor is ipilimumab, which is a fully humanized mAb that blocks the immunosuppressive signal by cytotoxic T-lymphocyte antigen 4. In 2011, the US Food and Drug Administration approved the use of ipilimumab for the treatment of advanced metastatic melanoma. Then, nivolumab, which is a humanized mAb that blocks programmed death-1 (PD-1), was approved for use in the treatment of advanced melanoma in 2014 and of advanced non-small-cell lung carcinoma (NSCLC) in 2015 in Japan. Pembrolizumab, which is another anti-PD-1 antibody, was approved for use in the treatment of advanced melanoma and advanced NSCLC as the first-line therapy in 2016 in Japan. Thereafter, nivolumab was also approved for use in the treatment of advanced renal cell cancer in August 2016, of Hodgkin's lymphoma in December 2016, and of head and neck cancer in March 2017 in Japan. Moreover, phase III trials of anti-PD-1 mAb and anti-PD-ligand 1 mAb for use in the treatment of cancers, such as gastric, ovarian, bladder, and esophageal cancers, are ongoing. Several clinical trials have investigated new agents, alone and in combination, for use in the treatment of various cancers including Hepatocellular carcinoma. Current advances in tumor immunology have unveiled the importance of immunosuppressive cells, such as regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages, especially in a tumor microenvironment (TME). Recent data suggest the inhibition of immunosuppressive cells and the cytokines related to them activate and infiltrate cytotoxic T cells and in TME, which could be one of the next combination strategies. The current clinical development of and future challenges in utilizing immune checkpoint inhibitors are presented.

S9-6

Immunotherapy for HCC

Stephen L. Chan¹

¹The Chinese University of Hong Kong, Hong Kong

Hepatocellular carcinoma (HCC) is no longer considered a cancer with limited option of drug treatment. Apart from multi-targeted kinase inhibitor, recent clinical data on the use of check-point inhibitors indicate that activation of adaptive immune system could induce treatment response safely in patients with HCC. Completed phase II clinical trials including the Checkmate 040 and the Keynote 224 study showed that monotherapy with PD-1 antibody could lead to response in approximately 15% of patients with advanced HCC, while approximately 40% of patients had durable stable disease after treatment. To confirm the benefits of PD-1 antibody, a number of phase III clinical trials have been designed to directly compare PD-1 antibody to sorafenib in first-line setting, or to placebo in the second-line setting. However, the enthusiasm was cooled down a bit by recent results of phase III clinical trials. In the lecture, I shall go over potential reasons explaining the difficulty in obtaining positive results in phase III clinical trials on PD-1 antibody in HCC. One of the solutions is to improve the proportion of patients benefitted by combinational therapy with PD-1 antibody and other agents, which include CTLA4 antibody and anti-angiogenic targeted therapy, which will be highlighted in the lecture. Finally, potential predictive biomarkers for immunotherapy will also be discussed in the lecture.

S9-7

How to Pick and Choose and How to Sequence Checkpoint Inhibitors Among All the New Advanced Hepatocellular Carcinoma Treatments

*Abou-Alfa Ghassan*¹

¹Memorial Sloan Kettering Cancer Center, USA

Tyrosine kinase inhibitors are now a standard of care therapy in first line and beyond for hepatocellular carcinoma. This is based in successful overall survival outcome in multiple phase III clinical trials for advanced hepatocellular carcinoma. After the advent of sorafenib more than a decade ago, four new tyrosine kinase inhibitors, lenvatinib in first line, regorafenib in second line after progression on sorafenib, cabozantinib beyond progression, and ramucirumab in patients with alpha fetoprotein greater than or equal to 400 ng/mL, have shown positive outcomes and several have already been established as approved standards of care and others way are on the way. The question remains on how to select among those agents.

Checkpoint inhibitors e.g. nivolumab and pembrolizumab have also shown and gained conditional approval for the treatment of hepatocellular carcinoma based on improved and extended response rates. Yet both have been reported to fail to show an improvement in overall survival in first line (nivolumab) and second line (pembrolizumab). While one may wonder if the nivolumab versus sorafenib in first line setting could be expected to fail considering that patients on the sorafenib arm may be treated with a checkpoint inhibitor later on, but how about pembrolizumab versus placebo in second line setting?

Would the answer be in a patient selection, more precise sequencing, or simply we need to explore further options of combining different checkpoint inhibitors like tremelimumab and durvalumab in the Himalaya Study, and/or the addition of checkpoint inhibitors to anti-angiogenic agents or tyrosine kinase inhibitors like pembrolizumab plus lenvatinib among many others.

Symposium 10: Cutting Edge of Diagnosis

S10-1

Computational Medicine in Muscle Segmentation and Quantification: Application to Survival Analysis in Patients with Advanced Hepatocellular Carcinomas

Chih-Horng Wu¹

¹National Taiwan University Hospital, Taiwan

Sarcopenia is associated with liver cirrhosis and hepatocellular carcinoma. In the past, body mass index, mid-upper-arm circumference and serum albumin are used to evaluate nutrition status. We also can use bioelectrical impedance analysis to measure body composition but the procedure is also affected by subcutaneous edema and ascites. In contrast, cross-section imaging such as computed tomography (CT) can analyze our body into total skeletal muscle (TSM), visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) quantitatively with high reproducibility and accuracy.

However, the segmentation and quantification of TSM takes a lot of time. Our study focuses on the automatic segmentation via machine learning and deep learning approaches. We used the trainable Gaussian smoothing filter to reduce noise and trainable gradient operator to detect margin. In this way, we only need acceptable data and available commercial GPU to complete the training with efficiency. There is high overlapping rate between of preprocess deep learning and manual tracking.

Finally, we analyzed patients who received first-line sorafenib therapy for advanced HCC in a prospective patient cohort between 2007 and 2012. The TSM, paraspinal muscle, psoas muscle (PM), rectus abdominis, and abdominal wall muscle areas were evaluated using a single CT slice at the third lumbar vertebra before treatment. We found that sarcopenia defined by TSM and PM and indices are independent predictors for poor prognosis of advanced HCC.

S10-2

Cutting Edge Diagnosis

Jeong Lee¹

¹Seoul National University Hospital, Department of Radiology

Hepatocellular carcinoma (HCC) can be noninvasively diagnosed on the basis of its characteristic imaging findings of arterial phase enhancement and portal/delayed “washout” on computed tomography (CT) and magnetic resonance imaging (MRI) in cirrhotic patients. However, different specific diagnostic criteria have been proposed by several countries and major academic societies. In 2018, major guideline updates were proposed by the Association for the Study of Liver Diseases, European Association for the Study of the Liver (EASL), Korean Liver Cancer Association and National Cancer Center (KLCA-NCC) of Korea. In addition to dynamic CT and MRI using extracellular contrast media, these new guidelines now include magnetic resonance imaging (MRI) using hepatobiliary contrast media as the first-line diagnostic test, while the KLCA-NCC and EASL guidelines also include contrast-enhanced ultrasound (CEUS) as the second-line diagnostic test. Therefore, hepatobiliary MR contrast media and CEUS will be increasingly used for the noninvasive diagnosis and staging of HCC. In this review, we discuss the emerging role of hepatobiliary phase MRI and CEUS for the diagnosis of HCC and also review the changes in the HCC diagnostic criteria in major guidelines, including the KLCA-NCC practice guidelines version 2018. In addition, we aimed to pay particular attention to some remaining issues in the noninvasive diagnosis of HCC.

S10-3

Criteria Generated by Computed Decision Tree to Filter CT Images Effective for Showing Arterial Enhancement of HCCKazuhiko Ueda¹¹The Cancer Institute Hospital of Japanese Foundation for Cancer Research

This presentation will show you newly designed visual-inspection criteria to identify effective CT images for showing arterial enhancement of HCC that was generated by computing the data of 3087 ROIs obtained from 441 arterial-dominant-phase acquisitions of CT imaging.

Diagnosis of HCC can be established without biopsy when the arterial enhancement in CT images is present. The arterial enhancement, being transient, may fail to be captured if the arterial-phase CT images were not timed optimally. Absence of arterial enhancement caused by ineffective CT images may lead to false-negative interpretation. Whether an ideal scan-delay time for effective CT images capturing the transient arterial enhancement of HCC exists has not been determined. Additionally, the way to identify CT images for showing arterial enhancement of HCC from ineffective images has not been determined.

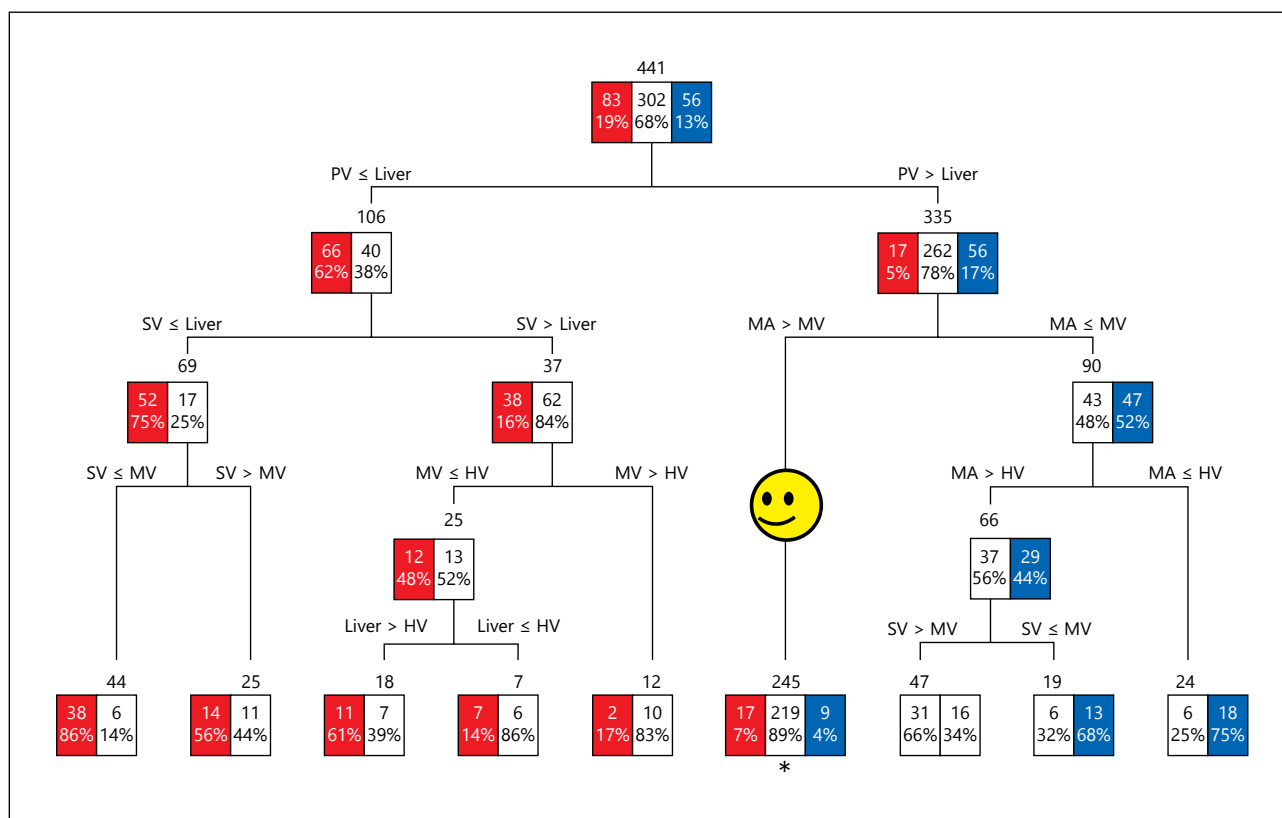


Fig. 1.

To design criteria to filter CT images effective for showing arterial enhancement of HCC, we measured attenuation values of seven sites: HCC; liver; superior mesenteric artery; and splenic, portal, superior mesenteric, and hepatic vein in CT images generated in seven 6-second-interval acquisitions completely covering the arterial-dominant phase. We defined as effective images those in which HCC attenuation minus hepatic attenuation exceeded 10 Hounsfield units, the threshold attenuation difference perceptible visually. Using the 3087 measurements, we selected an optimal variable set for identifying effective images by a decision tree created by recursive partitioning among 15 dichotomous independent variables: whether the attenuation difference between two sites among six: liver and the five vessels exceeds the threshold. We then compared positive predictive values (PPVs) for effective images with and without using the set using Student's t-test after computing standard errors by bootstrapping (1,000 replicates).

As a result, using the optimal set: portal vein and superior mesenteric artery were visually hyperattenuating to the liver and superior mesenteric vein, respectively: improved the PPV from 69% to 89% ($P < 0.001$).

In conclusion, arterial-dominant-phase CT images satisfying the criteria attenuation differences will show hypervascular HCCs as hyperattenuating to the liver; images not satisfying it may cause false-negative interpretation.

S10-4**Dual-Energy CT Applications in the Liver***Keitaro Sofue*¹¹Kobe University Graduate School of Medicine

Dual-energy computed tomography (DECT) requires the acquisition of two datasets utilizing two different x-ray energy spectra, which potentially enables to characterize different materials on the basis of their elemental composition. DECT provides several advantages over conventional single-energy CT technology because of its ability to distinguish between substances of sufficiently different x-ray energy attenuation. Consequently, DECT applications can generate virtual monochromatic images and material decomposition images with use of the known changes in attenuation between the two different spectra. Virtual monochromatic images can obtain different monoenergetic images, which enable to acquire the optimal energy images. Lower keV images can increase iodine attenuation and contribute to achieve higher lesion-to-liver contrast for the detection and characterization of the focal liver lesions. Material decomposition images basically aim to discriminate two or three different specific materials (eg, fat, calcium, iodine, and water). With use of material decomposition images, iodine density images can be generated and used to quantify the content of the iodine in the placed regions of interest. Moreover, material decomposition algorithm can be applied for the estimation of fat, iron, and so on. I would like to show the applications of the DECT techniques into the liver imaging with case presentation and reviewing the current topics.

S10-5

Cutting Edge of Liver Cancer Diagnosis by Intraoperative Ultrasonography

*Hideki Yokoo¹, Hagiwara Masahiro¹, Takahashi Hiroyuki¹,
Imai Koji¹, Matsuno Naoto¹, Furukawa Hiroyuki¹*

¹Asahikawa Medical University

Accurate detection and diagnosis are mandatory to treat hepatic malignancy. Many imaging modalities has been developed for this purpose including extracorporeal echocardiography, multiple detector computed tomography (MDCT), and gadoteric acid-enhanced magnetic resonance imaging (MRI). Intraoperative US has been shown to yield significant new information not identified on preoperative imaging. It has become a gold standard either to determine the resectability or to change the operative plan. Recently, to find occult hepatic lesions during hepatectomy for the patients with hepatic malignancy, contrast-enhanced IOUS (CE-IOUS) was performed using Sonazoid, a second generation ultrasound perflubutane microbubbles agent.

This cutting edge technology offers three advantages. Firstly, CE-IOUS is the most useful modality for accurate detection and diagnosis of hepatic tumors intraoperatively. In case of HCC, CE-IOUS can exclusively identify poorly differentiated or well-differentiated HCC, which is difficult to identify in ordinary IOUS. In cases of intrahepatic cholangiocarcinoma or metastatic liver cancer, even for tumors with unclear imaging in ordinary IOUSs, imaging in the Kupper phase with CE-IOUS is extremely clear and is useful for tumor identification and determination of the excision range.

Secondarily, CE-IOUS offers safe hepatectomy to demonstrate accurate resection margin. After portal pedicle ligation for anatomic resection, intravascularly administered Sonazoid provides a parenchymal-specific contrast image based on its accumulation in the Kupffer cells, and we were able to identify the parenchymal transactional line as the margin with loss of blood flow shown as a hypo-enhanced image for over 1 hour. Therefore, we were able to confirm the resection line of the parenchyma with IOUS in three-dimensional manner at any time.

Thirdly, CE-IOUS can confirm whether the adequate treatment is applied to the liver tumor to detect the size of treatment. CE-IOUS can be applied to the intraoperative evaluation of the ablation range of intraoperative microwave coagulation and radiofrequency ablation, which are used as adjunctive treatment to hepatectomy.

In conclusion, CE-IOUS is a promising technology to support all aspects from the diagnosis to the treatment of the hepatic malignancy.

S10-6

**Hemodynamic Characteristics of Intrahepatic
Cholangiocarcinoma and Cholangiolocellular Carcinoma
Using Contrast-Enhanced Ultrasonography**

Akiko Saito¹, Masakazu Yamamoto², Satoshi Katagiri², Shunichi Ariizumi²,
Masayuki Nakano², Masatoshi Makuuchi²

¹Japanese Red Cross Medical Center, ²Tokyo Women's Medical
University, Japan

Introduction: Hepatocellular carcinoma (HCC) is often detected during medical check-ups in patients with chronic liver disorders. However, occasionally mass forming type intrahepatic cholangiocarcinoma (mf-ICC) or cholangiolocellular carcinoma (CoCC) is discovered. As the prognosis differs markedly between these diseases, identifying the characteristics of these tumors is important, especially for determining optimal therapy. We examined the hemodynamics of mf-ICC and CoCC using contrast-enhanced ultrasonography (CEUS).

Method: CoCC was pathologically defined as showing positive staining for epithelial membrane antigen (EMA) on the luminal surfaces of tubules. Among hepatic nodules examined by CEUS since December 2000, 11 mf-ICC and 12 CoCC were selected based on pathological findings that had been surgically confirmed. After Levovist or Sonazoid was administered intravenously, arterial phase imaging from 1 to 50 sec and subsequent enhancements up to 30 min were observed.

Results: Tumors were ≤ 3 cm in 50% of CoCC and 27% of mf-ICC. All CoCC and 64% of mf-ICC were positive for either HBV or HCV. All tumors demonstrated some degree of positive enhancement. Mf-ICC had various patterns of enhancement but more than half (64%) showed peripheral enhancement. In contrast, 83% of CoCC showed whole-tumor enhancement. In the arterial phase, the feeding artery or tumor enhancement was well visualized in 55% of mf-ICC, while tumor enhancement other than of the feeding artery was clear in 92% of CoCC. In subsequent phases, all mf-ICC showed washout within 1 min, while washout was slightly delayed in CoCC up to 3 min. There was no relationship between enhancement grade and tumor size in either CoCC or mf-ICC.

Conclusion: CoCC showed whole-tumor enhancement that was slightly prolonged as compared to that of mf-ICC. Considering the additional findings of smaller tumors and the higher rate of hepatitis virus marker positivity, CoCC has characteristics more like those of typical HCC.

Symposium 11: Liver Transplantation for Primary Liver Cancer

S11-1

Better Recipient Selection and Allograft Quality in a World of Limited Resources

*Koji Hashimoto*¹

¹Cleveland Clinic

Liver transplantation offers the best chance of long-term survival for select patients with early-stage hepatocellular carcinoma (HCC). In a landmark 1996 study, tumor morphology was shown to be an important factor determining transplant outcomes. Since the Milan criteria have become the standard for determining eligibility for liver transplantation, moderate expansions for the criteria have been reported with or without incorporating tumor biology. Such approaches have increased the number of eligible patients for transplant with an increased risk of tumor recurrence. Further, most of these models were dichotomous or not validated with large national datasets. The other important consideration in liver transplantation for HCC is organ allocation where the MELD score determines the priority to receive deceased donor organs. Therefore, the ideal model for patients with HCC is a continuous score that takes all 3 factors (tumor morphology, biology, and background liver disease severity) into account. In 2017, we developed a continuous score, HALT-HCC (Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma), based on 420 liver transplant recipients for HCC at Cleveland Clinic and validated this model with US national data (SRTR, n = 13,717). This new continuous score is statistically and clinically superior to other models in discriminating patients with poor survival. In addition to better recipient selection, increasing donor volume is an important mission in liver transplantation for HCC. Since there are not enough donor livers, extended criteria donor grafts and technical variant grafts have been utilized. Although opportunities for transplant have increased, the effect of these “non-standard” liver grafts on patients with HCC is still controversial. Finally, recent studies have shown that the degree of graft injury determined by ischemia time and graft hemodynamics (intraoperative portal flow and hepatic artery flow) is associated with an increased risk of tumor recurrence. With accumulating worldwide experiences in liver transplantation for HCC, it is essential to take multiple factors into account to achieve better outcomes than ever before.

S11-2

Liver Transplantation for Primary Liver Cancer

Kyung-Suk Suh¹

¹Seoul National University Hospital

Liver transplantation (LT) is one of the accepted treatment modalities for hepatocellular carcinoma (HCC). In 1996, Mazzaferro *et al.* suggested that LT should be limited to patients with early HCC characterized by no major vessel invasion and a single tumor less than 5 cm in size, or three or fewer tumors with the largest tumor less than 3 cm in size, referred to as the Milan criteria. They showed that good 4-year overall and recurrence-free survival rates of 75 and 83% respectively, were obtained when LT was performed for early HCC. These Milan criteria are even now widely used to identify suitable candidates for LT with a good prognosis. Nonetheless, many investigators have pointed out that the Milan criteria are too restrictive. Hence, variable expanded criteria for LT for HCC have been suggested. However, it is still unclear which criteria are the most effective for selecting good candidates. In addition, there is no consensus on the acceptable patient survival after LT, especially living donor liver transplant (LDLT).

LDLT became one of the important treatment modalities for hepatocellular carcinoma HCC in Asian countries. LDLT for HCC has been increasing and it has recently accounted for about 50% of adult LDLT in our center. The classical indication of LT for HCC in Asian countries is early staged HCC with poor liver function. For resectable cases with good liver function, resection instead of primary LDLT is considered first in most Asian countries. The Milan or UCSF criteria were still used as a selection criteria even in LDLT. However, its indication has been expanded in LDLT because a living graft is dedicated to only one recipient. Recently, the indication of LDLT for HCC has expanded selectively and experience in advanced stage and/or good liver function has accumulated in our center. The tumor biology is important to select optimal indications of LDLT for HCC. Size and number are not enough to stratify the prognosis in LDLT. New biological criteria based on AFP, PIVKAI and PET positivity seemed better to exclude futile LDLT.

S11-3

The effect of Bridging or Downstaging on Survival Outcomes after Liver Transplantation for HCC

Ki-Hun Kim¹

¹Asan Medical Center/Ulsan University

Objective: We evaluated the long-term outcomes of patients who underwent liver transplantation (LT) with or without bridging or downstaging for hepatocellular carcinoma (HCC).

Summary of Background Data: There is no consensus regarding selection criteria on LT for HCC, although emerging evidences has been found for the effectiveness of bridging or downstaging.

Methods: This retrospective study included 896 LT recipients with HCC between June 2005 and May 2015. Recurrence-free survival (RFS), overall survival (OS), and their associated factors were evaluated.

Results: The 5-year RFS in the full cohort of 896 patients was 82.4% and the OS was 85.3%. In patients with initial Organ Procurement and Transplantation Network (OPTN) T1 and T2, the 5-year RFS and OS did not significantly differ between LT groups with and without bridging (all $P \geq 0.05$). The 5-year RFS and OS of OPTN T3 patients with successful downstaging were not significantly different from those with OPTN T2 with primary LT ($P = 0.070$ and $P = 0.185$), but were significantly higher than in patients with OPTN T3 with downstaging failure and initial OPTN T1 or T2 with progression (all $P < 0.001$). In the multi-variable analysis, last AFP before LT ≥ 70 ng/mL (hazard ratio [HR], 1.77, $P = 0.001$ and HR, 1.72, $P = 0.004$), pretransplant HCC status exceeding the Milan criteria (HR, 5.12, $P < 0.001$ and HR, 3.31, $P < 0.001$), and positron emission tomography positivity (HR, 2.57, $P < 0.001$ and HR, 2.57, $P < 0.001$) were independent predictors for worse RFS and OS.

Conclusions: OPTN T3 should undergo LT after successful downstaging. OPTN T3 with successful downstaging allows for acceptable long-term post-transplant outcomes.

S11-5

New Japanese Expanded Criteria, “5-5-500 Rule”, for Liver Transplant Candidates with HCC

Nobuhisa Akamatsu¹, Tsuyoshi Shimamura², Hiroto Egawa³,
Hideki Ohdan⁴, Shinji Uemoto⁵, Kiyoshi Hasegawa¹, Norihiro Kokudo⁶

¹The University of Tokyo, ²Hokkaido University Hospital, Japan, ³Tokyo Women Medical University, Japan, ⁴Hiroshima University Hospital, Japan, ⁵Kyoto University Hospital, Japan, ⁶National Center for Global Medicine, Japan

Expansion of the liver transplantation indication criteria for patients with hepatocellular carcinoma (HCC) has long been debated. Here we propose new, expanded living-donor liver transplantation (LDLT) criteria for HCC patients based on a retrospective data analysis of the Japanese nationwide survey. A total of 965 HCC patients undergoing LDLT were included, 301 (31%) of whom were beyond the Milan criteria. Here, we applied the Greenwood formula to investigate new criteria enabling the maximal enrollment of candidates while securing a 5-year recurrence rate (95% upper confidence limit) below 10% by examining various combinations of tumor numbers and serum alpha-fetoprotein (AFP)/des-gamma-carboxy prothrombin (DCP) values, and maintaining the maximal nodule diameter at 5 cm. Finally, new expanded criteria for LDLT candidates with HCC, the 5-5-500 rule (nodule size 5 cm in diameter, nodule number 5, and AFP 500 ng/ml), were established as a new regulation with a 95% confidence interval of a 5-year recurrence rate of 7.3% (5.2–9.3), achieving the maximal number of eligible patients by 19% increase. In addition, the 5-5-500 rule could identify patients at high risk of recurrence, among those within and beyond the Milan criteria. The recurrence free survival by each criteria and 5-year patient survival/recurrence rate were presented in the table. In conclusion, the new criteria the 5-5-500 rule might provide rational expansion for LDLT candidates with HCC.

Table 1.

Criteria	5-year survival (%)	5-year recurrence rate (%)
Within Milan	75.3	7.5
Within 5–5-500	75.8	7.3
Within Milan or 5–5-500	74.8	9.1
Within Milan/Within 5–5-500	76.5	5.2
Within Milan/Beyond 5–5-500	62.5	32.5
Beyond Milan/Within 5–5-500	72.6	17.2
Beyond Milan/Beyond 5–5-500	48.6	47.8

Symposium 12: Radiotherapy for Hepatocellular Carcinoma

S12-1

Radiotherapy, Where It Stands in Guidelines for Hepatocellular Carcinoma Treatment

Jinsil Seong¹

¹Yonsei University

External beam radiotherapy (EBRT) is a well-established cancer modality in most major solid cancers. In hepatocellular carcinoma (HCC), its role hasn't been fully recognized due to lack of high level evidence. However, its efficacy has been witnessed by soaring number of papers reporting beneficial clinical outcome as well as increasing level of evidence. EBRT can be administered in various ways depending tumor stage as well as treatment aim; for small tumors in BCLC early stage, radiotherapy can be given in curative aim. High dose focal radiation is delivered in short term, which is referred to stereotactic ablative radiotherapy (SABR) or stereotactic body radiotherapy (SBRT). It needs precision technology involving image-guided beam delivery (image guided radiotherapy) as well as motion control.

For HCC beyond early stage, EBRT can be given using conventional or hypofractionation scheme, which is adopting preferably combination scheme with other modality, either as an additional treatment for HCCs showing incomplete result to TACE or as a combination of EBRT and vascular therapy for HCC accompanying vascular invasion. Although HCC beyond the early stage is considered ineligible for curative resection, EBRT-based combination approach can achieve substantial down-staging or down-sizing, so that subsequent curative resection could be underwent. Therefore, radiation therapy can be adopted as a curative intent in management of HCC either by ablative radiotherapy for early stage HCC or by combination approach converting substantial number of patients to resectable ones in HCC beyond the early stage.

Consequently major treatment guidelines either include EBRT as one of the treatment options or just mention depending on disease status. In this presentation, radiotherapy in current guidelines for HCC treatment will be discussed.

S12-2

Downstaging to Surgical Resection in HCC the NCCS Experience with Yttrium-90 and Immunotherapy

Pierce Chow^{1,2,3}

¹National Cancer Centre Singapore, ²Singapore General Hospital, ³Duke-NUS Medical School

While surgical resection is potentially curative in early stage hepatocellular carcinoma (HCC), most patients with HCC present at the intermediate stage where surgery either cannot be carried out or cannot be carried out with a curative intent. The standard of care for intermediate stage HCC is thus loco-regional therapy and that for advanced HCC is systemic therapy.

Recent developments in loco-regional therapy in the form of selective internal radiation (SIRT) with yttrium-90 and in systemic treatment in the form of immunotherapy have shown significantly improved efficacy with both these modalities. With these improved efficacies, patients who presented with HCC at a stage where curative surgical resection was not possible, may now have the opportunity to undergo potentially curative surgical resection after successful downstaging with both SIRT and immunotherapy.

We share the experience of the NCCS in downstaging HCC to surgical resection with SIRT and immunotherapy.

S12-3

Proton Beam Therapy for Liver Tumors

Hideyuki Sakurai¹, Toshiyuki Okumura¹, Haruko Numajiri¹,
Yuta Sekino¹, Takashi Izumi¹, Shousei Shimizu¹, Masashi Mizumoto¹,
Keiko Murofushi¹, Kayoko Ohnishi¹, Kei Nakai¹, Hitoshi Ishikawa¹

¹University of Tsukuba

Common radiation therapy (RT) using X-ray with conventional fractionation is not curative enough for the primary liver tumors. Therefore, it has not been performed as a high priority in comparison to other standard treatments, such as surgery, ablation and transcatheter approach. Since the normal liver tissue shows high sensitivity to radiation, especially for patients with liver cirrhosis, non-irradiated normal liver volume must be preserved as much as possible when curative radiation is given for the liver tumors. In recent years, many technological progress has been made in radiation oncology, RT has been used as an important curative treatment option for liver tumors with several conditions. Stereotactic body radiotherapy (SBRT) is a technique to concentrate radiation doses three-dimensionally on small target, with short-term irradiation of 1–2 weeks. The SBRT can be used for small tumors less than 5 cm with about 90% local control. Particle beam therapy (PBT; proton beam therapy, heavy ion beam therapy) has unique character of radiation dose distribution, which is called “Bragg peak”. PBT can accumulate more dose to the target with minimizing normal liver dose, even though the large tumor exists. Recently, primary liver tumor is an important indication, and it has been specified to be of the highest priority by the American Society for Radiology and Oncology (ASTRO) model policy. PBT for the liver tumor has been initially developed in Japan, and many relevant clinical studies were performed at the University of Tsukuba. The eligibility criteria for PBT of hepatocellular carcinoma (HCC) include Child-Pugh classification A or B, 3 nodules or less, and tumor sizes up to 15 cm. Most of the cases were considered to be inappropriate for local tumor control using other standard treatment modalities. The local control rate was approximately 90% and the 5-year survival rate was reported to be approximately 50%. Clinical studies of PBT report favorable therapeutic effects, even for not only large tumors but also tumors in elderly patient. In addition, PBT has been clearly shown to play an important role in the treatment of HCC-related portal vein tumor thrombosis (PVTT). Clinical data with PBT have been accumulating and are expected to be incorporated into the standard treatment of hepatocellular carcinoma.

S12-4**Carbon Ion Radiotherapy for Hepatocellular Carcinoma***Kei Shibuya¹, Tatsuya Ohno¹*¹Gunma University Heavy Ion Medical Center

Particle therapy with protons and carbon ions allows a unique precision in delivering a high dose to the target tumor, while sparing the surrounding healthy tissues, compared with photon therapy. Carbon ion beams provide improved physical dose distributions owing to the high relative biological effectiveness of linear energy transfer. In contrast to neutron beams, which has uniformly high linear energy transfer at all depths, the linear energy transfer of carbon ion beams increases steadily with depth, reaching a maximum at the peak region. For carbon ions, the relative biological effectiveness in the target region can be 2–3 times higher than photon therapy and is influenced by many factors, such as dose, energy, and biological system. Therefore, carbon ion radiotherapy is expected to be effective against intractable, photon-resistant cancers.

In Japan, at the National Institute of Radiological Sciences of Chiba, clinical trials with carbon ion radiotherapy were firstly begun in 1994. Then, five centers including Gunma University Heavy Ion Medical Center initiated the treatment. In 2014, the Japan Carbon-ion Radiation Oncology Study Group (J-CROS) was formed to conduct multi-center clinical studies on various cancer sites. At first, we evaluated the effectiveness and safety of short-course carbon-ion radiation therapy for hepatocellular carcinoma in a multicenter study. A total of 174 patients were enrolled. Prescribed C-ion RT doses were 48.0 Gy (relative biological effectiveness [RBE]) in two fractions (n = 46), and 52.8 Gy (RBE) (n = 108) and 60.0 Gy (RBE) (n = 20) in four fractions. The median follow-up period was 20.3 (range, 2.9–103.5) months. The overall survival and local control rates at 1, 2, and 3 years were 95.4%, 82.5%, and 73.3%, and 94.6%, 87.7%, and 81.0%, respectively. No treatment-related death occurred during the follow-up period. Grades 3 or 4 treatment-related toxicities were observed in 10 patients (5.7%); RILD was observed in three patients (1.7%).

We would like to present recent accumulated clinical data and future perspectives on carbon ion radiotherapy for hepatocellular carcinoma.

Sponsored Symposium

SS1-1

Multipolar Radiofrequency Ablation Combined with 3D Sim-Navigator and E-Field Simulator

Hironao Okubo

Senior associate professor, Juntendo University Nerima Hospital,
Department of Gastroenterology

Radio frequency ablation (RFA) is recognized as a curative locoregional therapy for early stage hepatocellular carcinoma (HCC). In Japan, bipolar RFA procedure with Celon POWER became available in 2013. The novel RFA system has the advantage in producing a large volume of ablative zone for a larger tumor. In case of small HCC, it has the potential to prevent intrasubsegmental tumor recurrence after RF ablation by no touch ablation. Nevertheless, it requires considerable skill to insert multiple electrodes around the target tumors to get the adequate ablative zone. Thus, the institution using the multipolar RFA system has been decreasing in Japan.

ARIETTA 850, a new ultrasound system, bundles 3D Sim-Navigator and electric field (E-field) simulator through advances in function of Real-time Virtual Sonography (RVS). The positional relationship between the marked target and needle paths can be assessed in real time using the 3D body mark, reconstructed from the virtual CT volume data, with additional C-plane display orthogonal to the needle path. It provides simulation of multiple needle paths during navigation to a target with RVS. A color map superimposed on the CT image simulates the distribution of the electric field from the given location of multiple electrodes during RFA procedure. The simulation can be made with different positions of the multiple electrodes to determine the optimal arrangement. Advancements in real-time RFA needle guidance can bring significant improvements to the multipolar RFA technique.

SS1-2

Shift from “Simulation” to “Navigation” in Liver Surgery: Multimodality Fusion Using Augmented Reality Intraoperative Ultrasonography Assisted by Artificial Intelligence*Takeshi Takamoto*

National Cancer Center Japan, Division of Hepato-Biliary-Pancreatic Surgery

Preoperative computer simulation has enabled rehearsal of liver resection in virtual-reality space, assisting understanding individual liver anatomy and designing precise hepatectomy. However, there is still a long way to go for medical engineering to real-time navigate liver surgery. In practice, surgeons just look at operative field and imagine inside of the liver, using intraoperative ultrasonography (IOUS) and comparing the VH pictures in their brains. There is still no way of visualizing the location of tumors and intrahepatic vasculatures and the preoperatively designed liver transection line on the real liver.

To overcome this issue in liver surgery, we applied the newly developed ultrasound system, Real-time Virtual Sonography (RVS: Hitachi, Ltd., Tokyo, Japan), which provides automatic registration using artificial intelligence (RVS-AI). The RVS system uses a position sensor on the tip of IOUS probe and a magnetic field generator to obtain the coordinates and angle of the IOUS probe. In the AI-supported automatic registration, three-dimensional (3D) volume data of portal venous bifurcation is acquired by IOUS and is matched with CT volume data of the same anatomical parts, first. Then the system calculates the difference of 3D angles of the liver between the real-time IOUS and preoperative CT images. Finally, RVS-AI rotates and displays synchronized CT images next to the real-time IOUS images.

Although RVS-AI is still under development, we found four different ways of effective use as follows;

(1) Staining target guide: RVS-AI colors a target portal branch in the dye-injection anatomical segmentectomy. The target portal branch was marked in the preoperative VH in 3D simulation software. It was automatically reflected on the IOUS screen after automatic registration.

(2) Cut-here line: RVS-AI shows the VH-predetermined liver transection line. Surgeons can confirm the liver transection goes accurately on the designed line.

(3) Tumor detector: RVS-AI facilitates detecting a iso-echoic tumor or tumor-suspicious lesion which were pointed out and marked in preoperative imaging using 3D simulation software.

(4) Image browser: RVS-AI assists easy-reference of preoperative images from operative field. It provides preoperative CT or MRI images around the range of interest promptly.

At present, it seems that RVS-AI has potential to navigate liver resection as planned in VH. When the AI-assisted automatic registration develops and succeeds in decreasing spatial errors and shortening registration time, liver resection will be done more rapidly and more precisely.

SS2-1

Current and Future Treatment Strategy for TACE Failure or Refractoriness

Masatoshi Kudo

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

Transarterial chemoembolization (TACE) is a widely recommended treatment strategy for the intermediate-stage HCC. Treatment with TACE for intermediate-stage HCC is expected more than 2.5 years of survival. However, only few patients are expected to be completely cured with TACE and most need additional procedures. Palliatively repeated TACE may not only promotes resistance to TACE, but also leads to the deterioration of liver function.

The timing of conversion from TACE to sorafenib had been discussed repeatedly in Japan. The Japan Society of Hepatology (JSH) and the Liver Cancer Study Group of Japan (LCSGJ) proposed a clear definition of ‘refractoriness or failure to TACE’. Several studies in Japan validated that the conversion from TACE to sorafenib immediately after refractoriness to TACE is acceptable in terms of prolongation of overall survival. Recently, several guidelines have recommended that patients with intermediate-stage HCC are eligible for systemic therapy in the case of TACE treatment failure and refractoriness.

As for the next step, Intermediate-stage HCC is a largely heterogeneous disease that includes a subgroup of patients who do not benefit from TACE. The treatment strategy for this subgroup of patients currently remains an unmet need in clinical practice. The efficacy of combination therapy with TACE plus sorafenib (TACTICS trial) for the intermediate-stage was firstly demonstrated at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI) Symposium in 2018. In the TACTICS trial, PFS was significantly longer with TACE plus sorafenib than with TACE alone (25.2 months vs. 13.5 months). Therefore the combination therapy would be a new option of the intermediate-stage HCC treatment.

SS2-2**Current and Future Therapy in Unresectable HCC***Peter R. Galle*

University Medical Center Mainz, I. Medical Department, Mainz, Germany

Hepatocellular carcinoma shows a rising incidence in the Western world. The majority of diagnoses is made in advanced tumor stages when therapeutic options are limited. Despite significant efforts to develop and evaluate active compounds for systemic treatment in several randomized trials, to date only five drugs, sorafenib and lenvatinib in first-line, and regorafenib and cabozantinib in second-line, have been approved in Europe based on survival advantages in phase III clinical trials. In 2008 the multi-tyrosine kinase inhibitor sorafenib was the first systemic compound demonstrated to improve overall survival of patients with advanced HCC. Sorafenib acts by targeting multiple oncogenic signaling molecules (*i.e.*, VEGF, PDGFR, CKIT, BRAF) in cancer cells as well as the tumor microenvironment.

Since 2017 several phase III studies led to approval of new tyrosine kinase inhibitors in first and second-line settings. In 2016, the RESORCE trial assessing the efficacy and safety of regorafenib vs. placebo in patients who tolerated but progressed on sorafenib demonstrated a significantly improved time to progression (3.2 months vs. 1.5 months) as well as overall survival (10.6 months vs. 7.8 months) for patients treated with regorafenib.

More recently, in a randomized, open-label, phase III study, the multi-tyrosine kinase inhibitor lenvatinib, which targets VEGFR1–3, FGFR1–4, PDGFR α , RET, and KIT, was compared to sorafenib for unresectable HCC. This non-inferiority trial demonstrated a similar overall survival (13.6 months vs. 12.1 months; not significant) despite a significant increase in time to progression for lenvatinib (8.9 months vs. 3.7 months; $p < 0.00001$) in selected patients with less than 50% liver occupation, without obvious invasion of the bile duct, or invasion at the main portal vein.

In the second line setting, positive results from the phase III CELESTIAL trial, evaluating the multikinase-inhibitor, cabozantinib, in patients, who progressed on sorafenib, confirmed a prolonged overall survival (10.2 months vs. 8.0 months) and median progression free survival rates (5.2 vs. 1.9 months) compared to placebo. Besides these new multi-kinase-inhibitors with demonstrated clinical activity, the recent phase III REACH-2 study evaluating the efficacy of the monoclonal antibody against vascular endothelial growth factor (VEGF) receptor, ramucirumab in advanced HCC for the first time depicted a rationale for a biomarker driven therapeutic approach: After failure of the original REACH phase III study in unselected patients, the trial evaluated ramucirumab in patients with an elevated (>400 ng/ml) alpha-fetoprotein (AFP) level (NCT02435433) and confirmed improved overall survival in a second line setting.

In addition to TKIs, immune-oncological treatment strategies have entered the arena of HCC. Several clinical trials evaluate the efficacy of antibodies against

PD-1, PD-L1 and CTLA-4 both as mono-therapy as well as in combinatorial therapy approaches in patients with advanced HCC. The checkmate 040 phase II dose escalation and expansion trial for patients with advanced HCCs suggested safety and efficacy of the anti-PD-1 antibody nivolumab. Objective response rates of 15–20% were reached in patient cohorts including metastatic disease and previous treatment with sorafenib. Nivolumab could be used safely in uninfected and hepatitis C virus (HCV)- and hepatitis B virus (HBV)-infected HCC patients. The disease control rate reached 64% (95% confidence interval (CI) 58–71%) and the objective response rate was 20% (95% CI 15–26%) including 3 complete responses and 39 partial responses. Remarkable was a 9-month overall survival rate of 74% (95% CI 67–79%). Similar results have also been shown for other checkpoint inhibitors such as pembrolizumab and durvalumab alone or in combination with tremelimumab. In the KEYNOTE-224 study, mOS was similar to nivolumab in the second line at 12.9 months with a disease control rate of 61% and ORR of 18%. Based on these findings, nivolumab and pembrolizumab were approved by the FDA for second-line therapy of advanced HCC. Very recently, pembrolizumab was evaluated in the KEYNOTE-240 phase III study in patients with advanced hepatocellular carcinoma (HCC), who were previously treated with systemic therapy, compared to placebo plus best supportive care (NCT02702401). The study did not meet its co-primary endpoints of overall survival (OS) and progression-free survival (PFS). The negative results of this first phase III study of immune-therapy in HCC call into doubt general use of checkpoint-inhibition in unselected patients with advanced stages of the disease. Furthermore, according to a recent press release the checkmate 459 trial, investigating nivolumab against Sorafenib did not reach the pre-specified level of superiority in OS. Several trials currently investigate different combinations of IOs, TKIs and anti-angiogenic antibodies.

SS2-3

Real-World Evidences of Sorafenib-Regorafenib Sequence in the Management of Advanced HCC: From Clinical Trials to Daily Practice

Changhoon Yoo

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

Sorafenib-regorafenib sequence therapy has demonstrated its clinical benefit in the management of unresectable or metastatic hepatocellular carcinoma (HCC) through the success of a pivotal randomized phase 3 RESORCE trial. Because there exist discrepancies between the characteristics of patients in daily practice and clinical trials, review and understanding the results of real-world evidences of sorafenib-regorafenib sequence is important for the successful application of this strategy in the daily practice. At this presentation, Korean and Japanese retrospective analyses of regorafenib in advanced HCC will be reviewed.

SS3

Optimising Treatment Outcomes with Systemic Therapy for the Right Patients, at the Right Time

Masafumi Ikeda¹, Stephen Lam Chan², Masayuki Kurosaki³, Nanya Wang⁴

¹National Cancer Center Hospital East, Japan, ²The Chinese University of Hong Kong, Hong Kong, ³Musashino Red Cross Hospital, Japan, ⁴Cancer Center at The First Hospital of Jilin University, China

This symposium on 31st August 2019 at APPLE will be sponsored by Eisai, co-chaired by Dr. Norihiro Kokudo (Japan) and Prof. Arndt Vogel (Germany), and will bring together other international experts in the treatment of hepatocellular carcinoma.

The symposium has several objectives, the first of which relates to providing guidance on the transition from local regional therapies, such as TACE, to systemic treatment. Specifically, Dr Masafumi Ikeda (Japan) will offer his professional insights into the optimal time to move between these treatment modalities.

Thereafter, Dr Stephen Lam Chan (Hong Kong) will discuss patient selection for systemic therapy as opposed to LRT and provide an understanding of which patient characteristics could be associated with better clinical outcomes. Moreover, and just as importantly, he will discuss those characteristics that may be associated with worse outcomes thus helping to identify which patients are best suited to which treatment.

Real-world experience of lenvatinib use from Japan will then be presented by Dr Masayuki Kurosaki (Japan) showing how this experience compares to the data reported from the pivotal clinical trial, REFLECT. It will look at the efficacy outcomes being seen with lenvatinib but focus on a comprehensive review of the AEs observed in clinical practice whilst also providing guidance on AE prevention and management.

The symposium will conclude with a presentation on the optimisation of lenvatinib therapy illustrated by a number of clinical case studies from Dr Nanya Wang (China), providing examples of typical AEs seen in everyday practice and strategies used to manage them.

SS4

Role of the Liver Tumor Board in Early- and Intermediate-Stage HCC

Masatoshi Kudo¹, KwangHyub Han², Stephen Lam Chan³, Pierce Chow⁴

¹Kindai University, Japan, ²Yonsei University, Republic of Korea, ³The Chinese University of Hong Kong, China, ⁴National Cancer Centre, Singapore

The incidence of liver cancer is disproportionately high in the Asia-Pacific region compared with the rest of the world [1]. In 2018, 72.5% of all new cases of liver cancer, of which the primary type is hepatocellular carcinoma (HCC), were in Asia [1, 2]. Contrary to a rising global incidence, cases of HCC have stabilized in most Asian-Pacific countries over the past 20 years [2, 3]. In Japan, although HCC remains a major concern, incidence and mortality rates are in decline [3, 4]. The turnaround is in large part due to a combination of well-implemented surveillance initiatives, appropriate diagnostic algorithms, and effective management programs [2, 3]. A rising incidence of NAFLD/NASH will however contribute to more HCCs, potentially reversing this trend [5].

The prognosis of patients with HCC is greatly improved when detected and diagnosed at an early stage of disease advancement, given the availability of potentially curative treatments (e.g. surgical resection, local ablation, and liver transplantation) [2, 3]. For patients with intermediate-stage HCC, for whom curative therapy is not possible, transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) can provide locoregional tumor control and prolong survival [2]. The variety of treatment options necessitates collaboration between specialists from a number of disciplines, including hepatology, radiology, hepatobiliary surgery, and oncology.

The management of HCC is complex and highly individualized, and differences exist according to variations in local practice and variations in treatment guidelines across the Asia-Pacific region [6]. For this reason, it is important to delineate best practice and to share clinical experience from particularly challenging cases. In this symposium, we examine current treatment practices for the management of early- and intermediate-stage HCC across the Asia-Pacific region. Distinguished speakers from across Asia will describe the therapy area landscape, and present cases in order to explore the role of surgical resection/other therapies, ablation/TACE/TARE, locoregional therapies (LRT)/systemic therapies (with or without LRT), and when to start systemic therapy after LRT. The symposium will also draw upon the experiences of the panel of clinical experts to provide valuable insight into the role of the multidisciplinary liver tumor board in the management of early- and intermediate-stage HCC.

This symposium is organized and funded by AstraZeneca.

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Special Oral Session

SPS-001

CD47 Blockade Synergizes with PD-1 Checkpoint Inhibitor and Enhances Anti-Tumor Efficacy in Syngeneic Preclinical Model of Hepatocellular Carcinoma

Wonseok Kang¹, Ji-Young Kim¹, Sera Yang¹,
Sohee Kang¹, Yong-Han Paik¹

¹Samsung Medical Center, Sungkyunkwan University
School of Medicine, Seoul, Korea, Korea

Cancer immunotherapies targeting PD-1/PD-L1 immune checkpoint has shown great therapeutic efficacy by helping the adaptive immune system to recognize and attack cancer cells in hepatocellular carcinoma (HCC). However, a significant percentage of patients do not respond or develop resistance. Myeloid cells, including tumor-associated macrophages (TAMs), represent one of the most abundant immune cell types in HCC microenvironment and are often associated with a poor prognosis. CD47 expression on tumor cells protects from macrophage-mediated phagocytosis through interaction with SIRP-alpha expressed by myeloid cells. In this study, we investigated the effects of CD47 blockade in combination with PD-1 checkpoint inhibitor on the anti-tumor immune response in a syngeneic preclinical model of HCC. We found that the macrophage function, including phagocytic activity, was enhanced by CD47 blockade. This effect was further enhanced by co-treatment with PD-1 checkpoint inhibitor. In vivo, combination of CD47 and PD-1 blockades enhanced anti-tumor efficacy, in both tumor growth and survival. Collectively, our findings demonstrate that targeting CD47-SIRPalpha axis synergizes with PD-1/PD-L1 immune checkpoint inhibition and enhances anti-tumor efficacy in HCC.

SPS-002

Substantial Risk of Hepatocellular Carcinoma Recurrence Even After Five Years of No-Recurrence Period Among Early Stage Hepatocellular Carcinoma Patients Treated with Resection or Radiofrequency Ablation

Jihye Kim¹, Wonseok Kang¹, Dong-Hyun Sinn¹,
Geum-Youn Gwak¹, Yong-Han Paik¹, Moon Seok Choi¹,
Joon Hyeok Lee¹, Kwang Cheol Koh¹, Seung Woon Paik¹

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

Background/Aim: Although hepatocellular carcinoma (HCC) is notorious for its high recurrence rate, some patients do not experience recurrence for more than five years after resection or radiofrequency ablation for early stage HCC. Incidence and risk factors for HCC recurrence after five years of no-recurrence period remain unknown. The aim of this study was to identify the risk and risk factors of recurrence among patients who did not experience recurrence for long period. **Methods:** A total of 1451 consecutive patients (median: 55 years old, male: 79.0%, hepatitis B virus: 76.7%) with good liver function (Child Pugh class A) who were diagnosed with early stage HCC, and received radiofrequency ablation or resection as initial treatment between 2005 and 2010 were analyzed. Among them, 477 patients were alive and without recurrence at 5-years. **Results:** During a median follow-up period of 8.1 years, 961 patients (66.2%) experienced HCC recurrence. The cumulative recurrence rates at 2-year and 5-year were 39.2% and 57.8%, respectively. Of the 477 patients who were alive and without recurrence at 5-years, 122 patients (25.5%) experienced recurrence. For them, the next 5-year cumulative recurrence rate was 30%. While sex, albumin-bilirubin grade, alphafetoprotein (AFP) level, tumor number, maximal tumor diameter and treatment modality at diagnosis were associated with early recurrence (within 2 years), sex, fibrosis-4 (FIB-4) score, and AFP levels were associated with further HCC recurrence among patients who did not experience recurrence for more than five years. **Conclusion(s):** HCC recurrence rate was substantially high even after five years of no-recurrence period after HCC treatment. HCC patients warrant continued HCC surveillance even after five years of no-recurrence period, especially for men, high FIB-4 score, and elevated AFP levels at 5-years.

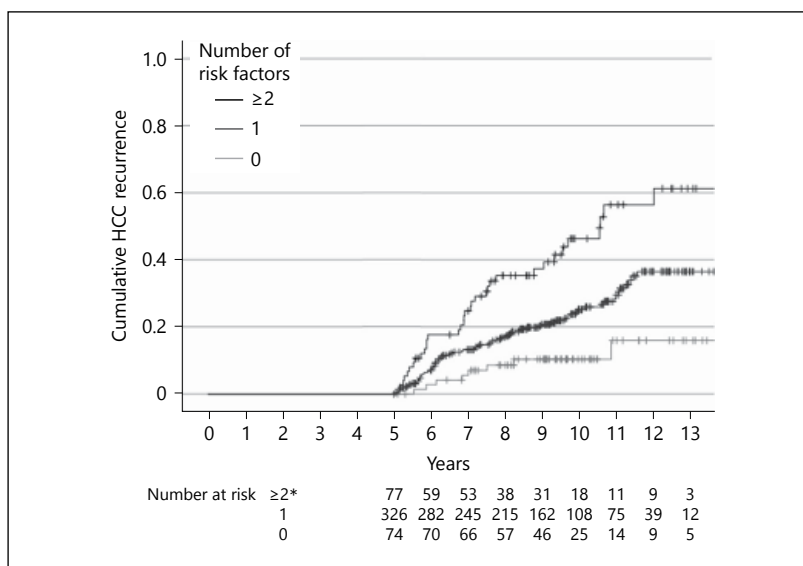


Fig. 1. (for Abstract no SPS-002).

SPS-003

Liver Transplantation (LT) for Hepatocellular Carcinoma (HCC): Impact of Indication Criteria and Tumor Markers for Recurrence

Akihiko Ichida¹, Nobuhisa Akamatsu^{1,2}, Harufumi Maki¹, Akiko Nakazawa¹, Sung Kwan Bae², Kayo Nojiri², Takeaki Ishizawa¹, Junichi Kaneko¹, Junichi Arita¹, Kiyoshi Hasegawa^{1,2}

¹Hepato-Biliary-Pancreatic Surgery Division, and Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Japan, ²Organ Transplantation Service, University of Tokyo, Graduate School of Medicine, Japan

Background: In our institute, Tokyo criteria (nodule size ≤ 5 cm in diameter and nodule number ≤ 5 , without macrovascular invasion) has been used as an indication criterion of LT for HCC patients. Recently we proposed a new criterion based on a Japanese nation-wide study, called 5-5-500 criteria (nodule size ≤ 5 cm, nodule number ≤ 5 , and AFP ≤ 500 ng/ml). In this study, we compared the indication criteria, such as Milan criteria, Tokyo criteria, and 5-5-500 criteria among our cohort. The usefulness of preoperative tumor markers was also evaluated. **Methods:** Between 1996 and 2018, 609 patients underwent living donor LT. Of these, 148 patients with HCC were evaluated. **Results:** Five-year survival rate after LT in HCC patients was 77%. HCC recurrence rate was 8.1% (12 cases) in all patients, 6.2% (9 of 142 cases) in patients meeting the Tokyo criteria, 4.5% (6 of 134 cases) in patients meeting the 5-5-500 criteria, and 6.3% (8 of 126 cases) in patients meeting the Milan criteria, respectively. ROC analysis for recurrence detection revealed that the best cutoff value of AFP, AFP-L3, and DCP was 253 ng/ml (AUC0.896),

35% (AUC0.731), and 161 mAU/ml (AUC0.670), respectively. As for the analysis of risk factors for recurrence, AFP ≥ 250 (P < 0.0001, HR32.0, 95% CI 9.48–145), AFP-L3 ≥ 35 (P = 0.001, HR9.6, 95% CI 2.64–34.6), DCP ≥ 160 (P = 0.003, HR5.8, 95% CI 1.84–19.5), beyond Tokyo criteria (P = 0.014, HR7.27, 95% CI 1.61–24.5), and beyond 5-5-500 criteria (P = 0.0001, HR11.4, 95% CI 3.56–36.7) were identified as risk factors. **Conclusions:** The recurrence rate of patients meeting the 5-5-500 criteria was the lowest. Regarding tumor markers, the AUC of AFP was the largest. The analysis of risk factors also revealed the usefulness of AFP and the 5-5-500 criteria.

SPS-004

A Metro-Ticket Approach to Identify Candidates Beyond Milan Criteria Who Benefit From Surgical Resection for HCC

Pearly Quek^{1,2}, Ye Xin Koh³, John C Allen Jr.⁴, Reiko W.T. Ang¹, Brian K.P. Goh³, London P.J. Ooi⁵, Chung Yip Chan³, Alexander Y.F. Chung³, Ser Yee Lee³, Peng Chung Cheow³, Prema Raj Jeyaraj³, Jin-Yao Teo³, Juinn-Huar Kam³, Sabino Zani Jr.⁶, Dimitrios Moris⁶, Pierce K.H. Chow^{1,3}

¹Department of Surgical Oncology, National Cancer Centre Singapore, Singapore, ²College of Medical, Veterinary and Life Sciences, University of Glasgow, UK, ³Department of Hepatopancreatobiliary and Transplant Surgery, Singapore General Hospital, Singapore, ⁴Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore, ⁵Department of General Surgery, Singapore General Hospital, Singapore, ⁶Department of Surgery, Duke University Medical Centre, Durham, NC, USA

Background/Aim: Surgical resection (SR) is curative in early HCC and potentially extends life in intermediate stage HCC. Newer therapies including immunotherapy and Y90 also provide good outcomes in intermediate-stage HCC and there is a need to justify selection of patients with intermediate-

stage HCC who will benefit from SR. We applied a Metro-ticket approach to predict overall survival for SR in HCC over a wide range of tumor burden. **Methodology:** Survival data of patients with SR for HCC from 1st January 2000 to 30th June 2016 at the Singapore General Hospital/National Cancer Center Singapore were analyzed. Inclusion criteria were histologically-proven HCC and a minimum follow-up period of 5 years or death within 5 years. Pre-operative imaging and post-operative pathology were correlated. Patients were stratified by alpha-fetoprotein (AFP) and tumour burden index (TBI) comprising size of largest nodule and number of nodules. 5-year overall survival (OS) of patients were mapped as smoothed bivariate contour plots with TBI against AFP, modelled after the Metro-ticket approach for liver transplantation (Mazzaferro et al., 2018). Bland-Altman plot was generated to investigate the difference between TBI from post-operative pathological measurements and pre-operative imaging. We validated the model with an independent cohort of 200 HCC resection patients from the Duke University Medical Centre. **Results:** 1121 patients underwent resection over this period and 601 met inclusion criteria. Scatter plot of TBI derived from pre-operative imaging and histology, generated a Pearson correlation coefficient $r = 0.93$. At TBI. **Conclusion:** A Metro-ticket model derived from TBI and AFP, allows robust comparison of OS after SR for HCC.

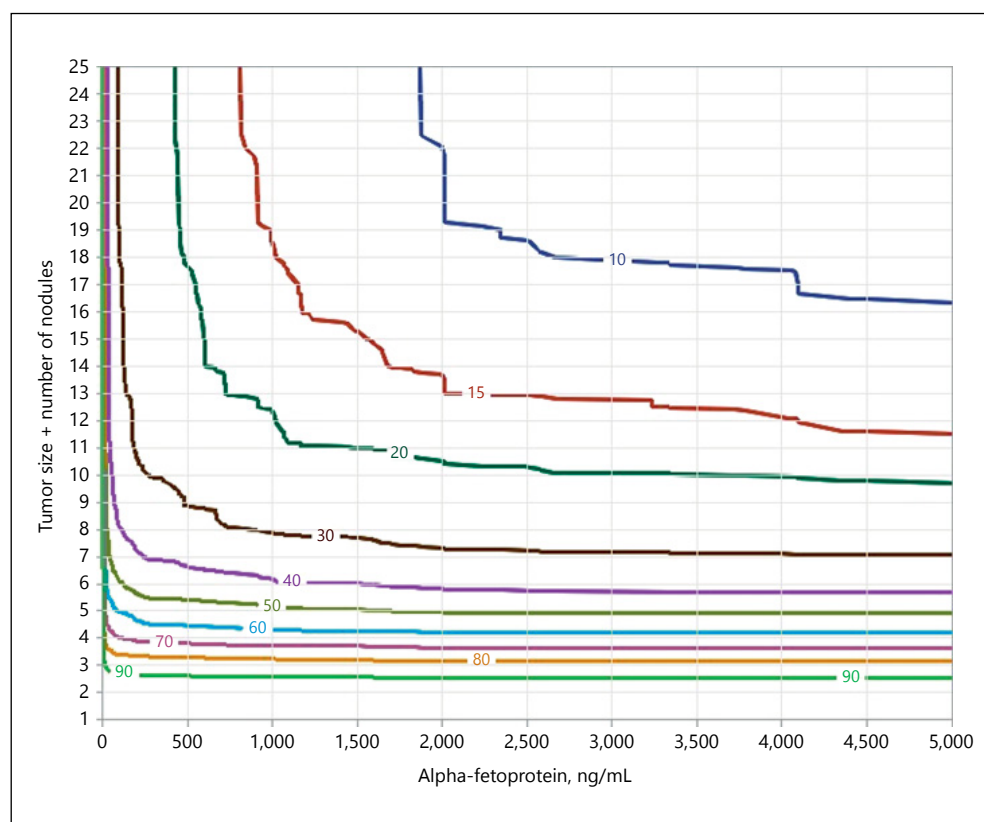


Fig. 1. (for Abstract no SPS-004).

SPS-005

A Multi-National, Multi-Institutional Study of Comparing an Efficacy of Stereotactic Body Radiation Therapy and Radiofrequency Ablation for Hepatocellular Carcinoma

Jinsil Seong¹, Nalee Kim¹, Jason Chia-Hsien Cheng², Wen-Yen Huang³, Tomoki Kimura⁴, Victor H.F. Lee⁵, Zhao-Chong Zeng⁶, Chul-Seung Kay⁷

¹Yonsei University College of Medicine, Korea,

²National Taiwan University Hospital, Taiwan, ³Tri-Service General Hospital, Taiwan, ⁴Hiroshima University Hospital, Japan, ⁵The University of Hong Kong, Hong Kong SAR, China, ⁶Fudan University, China, ⁷Incheon St. Mary Hospital, Korea

In the present study, we underwent a thorough analysis for comparing the effectiveness of SBRT to RFA in patients treated at 7 tertiary-referral hospitals. Patients treated for

HCC in 7 tertiary-referral hospitals were retrospectively reviewed. Among these, 1607 patients who underwent RFA of 1758 tumors and 505 patients who underwent SBRT of 519 tumors were included. Radiologic responses were evaluated using modified Response Evaluation Criteria in Solid Tumors to assess LC. Using propensity score matching (PSM) to adjust for clinical factors, 232 tumors were selected from each treatment arm. At baseline, SBRT-treated tumors were in more advanced BCLC stage, larger, and had a higher incidence of prior liver-directed treatments than RFA-treated tumors. The median follow-up period for the entire cohort was 31.4 (IQR, 14.1–45.7) months. The 3-year LC rates were 63.9% for tumors treated with SBRT and 66.6% for tumors treated with RFA, respectively ($p = 0.031$). In the univariate analysis for LC, tumor size, advanced stage, and serum AFP levels were attributed to local progression. However, treatment modality was significantly correlated with LC favoring SBRT (HR 0.74, p).

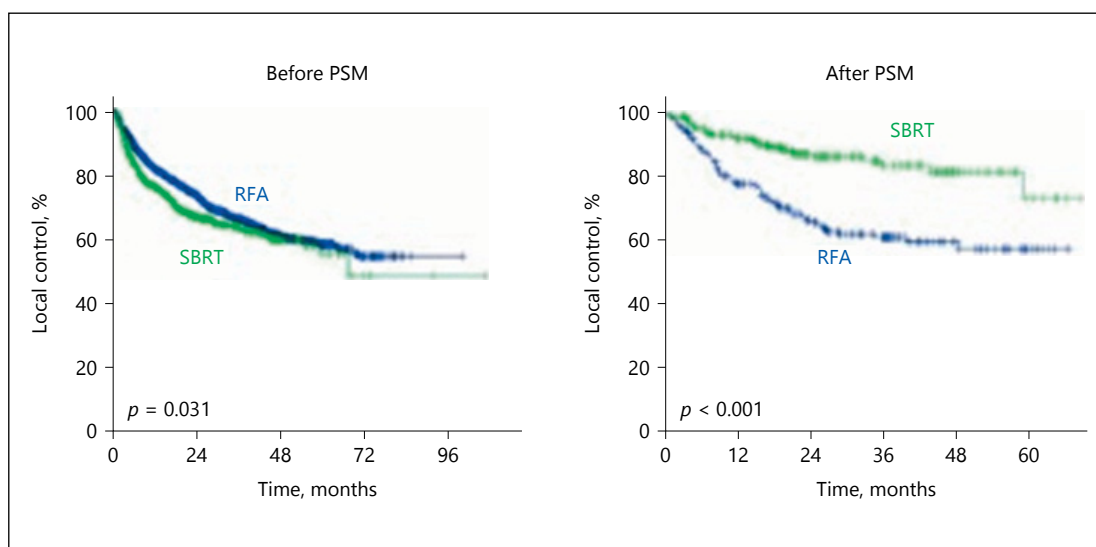


Fig. 1. (for Abstract no SPS-005).

Oral Session

Biomarkers / Cell Biology and Translational Research

O-001

Differential Expression of APE1 in Hepatocellular Carcinoma and the Effects on Proliferation and Apoptosis of Cancer Cells

Zhipeng Sun¹, Yubing Zhu¹, Amin Buhe¹, Qing Fan¹, Nengwei Zhang¹

¹Beijing Shijitan Hospital, Capital Medical University, China

This research aimed to investigate the differential expression of apurinic-apyrimidinic endonuclease 1 (APE1) in hepatocellular carcinoma (HCC) tissues and cells and the effects on proliferation and apoptosis of cancer cells. Immunohistochemical techniques were used to detect the expression of APE1 in 80 cases of HCC and the corresponding paracancerous tissue microarrays; meanwhile, Western blots were used to detect the expression of APE1 in both human HCC BEL-7402, BEL-7405, HCC-9204, Hep3B, HepG2, SMMC-7721, Huh-7 cells, and normal hepatocyte L-02 cells. The rela-

tionship between APE1 expression and clinical pathological characteristics of HCC was statistically analyzed. APE1 shRNA vector was constructed in Hep 3B cells to establish a stably transfected cell line, using Western blots to determine the interference efficiency. Cell proliferation activity was detected with MTT assays, while apoptosis was detected with the Annexin V-FITC/PI double-labeling technique. The expression of APE1 in HCC tissues and cells was significantly up-regulated, and its expression was significantly different from TNM staging and histopathological grading. APE1 expression in HCC cells was 2.5–3.6 times higher than in normal hepatocytes. Down-regulation of APE1 expression significantly reduced the proliferative activity and increased the apoptosis rate of Hep 3B cells. MTT assay results showed that the cell absorbance in blank group, control shRNA group and APE1 shRNA group was 1.525 ± 0.079 , 1.497 ± 0.072 and 0.981 ± 0.063 , respectively. The Annexin V-FITC/PI double-labeling results showed the apoptosis rate in blank group, control group and APE1 shRNA group was $9.91 \pm 0.61\%$, $10.96 \pm 0.75\%$ and $20.06 \pm 1.73\%$, respectively. In conclusion, APE1 demonstrates cancer progression potential at the clinical, tissue and cell level. It provides a new idea and theoretical basis for APE1-based clinical diagnosis, prognosis determination and molecular targeted therapy in treatment of HCC.

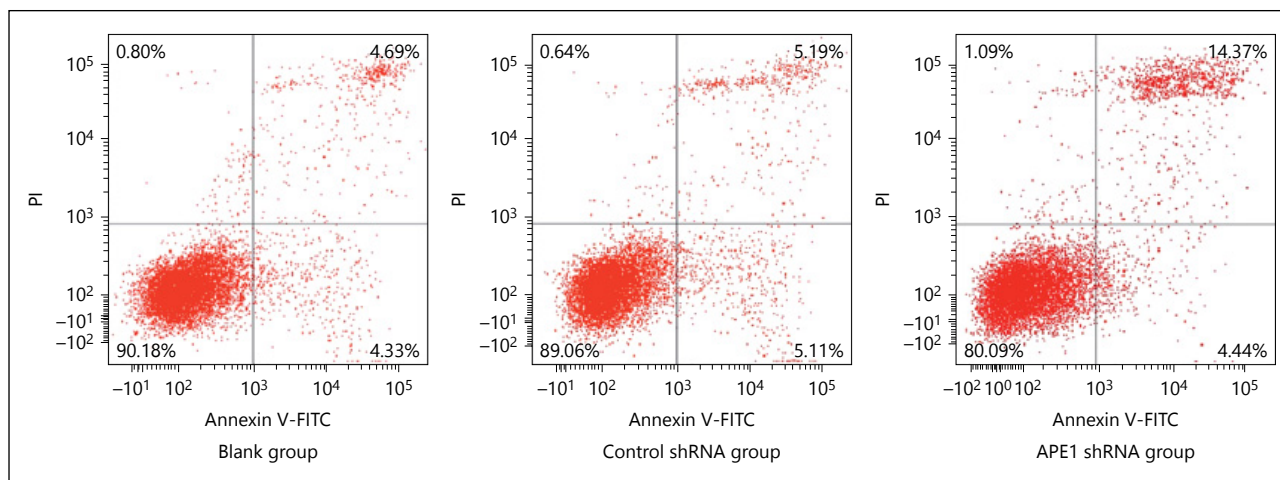


Fig. 1. Silencing APE1 significantly increases HCC Hep 3B cell apoptosis. Annexin V-FITC/PI double-labeling technique was used to detect apoptosis in each group. The results showed that the total apoptosis rate in blank group, control shRNA group and APE1 shRNA group was $9.91 \pm 0.61\%$, $10.96 \pm 0.75\%$ and $20.06 \pm 1.73\%$, respectively (for Abstract no O-001).

O-002

Histone Deacetylase 6 Suppresses CD47-Dependent Neoplastic and Anti-Phagocytic Behaviors of Hepatocellular Carcinoma

Suk Woo Nam¹, Hee Doo Yang¹, Hyung Seok Kim¹, Sang Yeon Kim¹, Min Jeong Na¹, Gyeongdeok Yang¹

¹The Catholic Univ of Korea, Korea

Histone deacetylase 6 (HDAC6) uniquely endows as tumor suppressor in hepatocellular carcinogenesis, but the underlying mechanisms leading to tumor suppression are not fully understood. To identify comprehensive microRNAs (miRNAs) regulated by HDAC6 in hepatocellular carcinogenesis, differential miRNA expression analysis of HDAC6-transfected Hep3B cells was performed. Using integrative analyses of publicly available transcriptome data and miRNA target prediction, we selected 5 miRNAs as a candidate and, through in vitro validation, showed that let-7i-5p specifically suppressed thrombospondin-1 (TSP1) in hepatocellular carcinoma (HCC). Ectopic expression of antisense let-7i-5p (AS-let-7i-5p) inhibited in vitro tumorigenesis of HCC cells. In addition, treatments of partially purified TSP1 from culture cell media (ppTSP1) and recombinant TSP1 (rTSP1) exhibited similar effects with AS-let-7i-5p treatment on the same HCC cells, whereas TSP1 neutralizing antibody treatment significantly attenuated these effects. Notably, treatments of HDAC6 plasmid, AS-let-7i-5p, ppTSP1 and rTSP1 significantly suppressed in vitro angiogenesis and metastatic potential of HCC cells, but the pre-treatment of antibody specific to CD47 receptor binding motif successfully blocked these effects in same cells. Furthermore, we demonstrated that recovery of HDAC6 elicited let-7i-5p suppression to de-repress the TSP1 expression, and thereby it occupied CD47 receptor to block CD47-SIRPα mediated anti-phagocytosis of macrophage in HCC. We also observed that HCC-derived exosomal let-7i-5p suppressed TSP1 of recipient hepatocyte cells. Treatments of HDAC6 plasmid, AS-let-7i-5p and rTSP1 suppressed tumor incidence as well as tumor growth rates in a spontaneous mouse HCC model. Our findings suggest that signaling HDAC6-let-7i-5p-TSP1 axis suppressed neoplastic and anti-phagocytic behaviors of HCC by interacting with cell surface receptor CD47 in HCC and neighboring cells of tumor microenvironment providing a novel therapeutic target for the treatment of liver malignancy and metastasis.

O-003

miR-34a-5p Regulated HCC Radioresistance by Directly Targeting c-MYC

Xiao-Mei Zhao¹, Zhao-Chong Zeng¹, Yuan Zhuang¹

¹Department of Radiation Oncology, Zhongshan Hospital, Fudan University, China

Background: Improve the radio-sensitivity of HCC to achieve curative effects in a lower dose range and effectively protect the surrounding vital organs is an urgent clinical challenge, therefore, identifying novel factors or mechanisms involved in radioresistance might provide scientific evidence for individualized radiotherapy regimens for patients with HCC. **Methods:** We established two HCC radioresistant (HCC-RR) cell lines by pooling the colonies after repeated colonies formation assay. miRNA expression profiles of 7721-RR and 7721-parental (7721-P) cell line were performed to identify novel factors involved in HCC radioresistance. In the further mechanism study, we used method such as RT-PCR, western blot, colony formation, RNAi, luciferase report assay system. **Results:** The established HCC-RR cells displayed significantly higher survival fractions compared with HCC-P cells, which indicated we successfully established HCC radioresistant cell lines. Through the array-based human miRNA expression profiles of 7721-RR and 7721-parental cell line, we identified miR-34a-5p, a miRNA down-regulated in HCC-RR cell lines, and with the potency to enhance HCC radiation response in vitro, miR-34a-5p mimic transfection result in 7721 cell viability inhibition and survival fraction reduction in HCC after irradiation. In the further mechanism study, we found that miR-34a-5p regulated HCC radioresistance by directly targeting c-MYC, and c-MYC mediates radioresistance in HCCs through regulation of CHK1 and CHK2. We also measured the expression of miR-34a-5p/c-MYC at different time point in the process of HCC-RR establishment. The stable radioresistance HCC cell line (HCC-RR) and HCC cell line with no routine radiation after the radiation clonogenic selection (HCC-NRR), As the clonogenic assay revealed, HCC-NRR cells exhibit obviously radiosensitivity restore compared with HCC-RR. Further analysis showed that HCC-RR cells exhibit significant upregulation of c-MYC but downregulation of miR-34a-5p, whereas HCC-NRR exhibit upregulation of miR-34a-5p, and smooth decline of c-MYC. These findings suggested that persistent irradiation enhance radioresistance of HCC cell line may through miR-34a-5p/c-MYC pathway.

O-004

The Molecular Mechanism of LncRNA34a-Mediated Regulation of Bone Metastasis in Hepatocellular Carcinoma

Li Zhang¹, Niu Hao¹, Jie Ma¹, Bao-Ying Yuan¹, Yu-Han Chen¹, Yuan Zhuang¹, Gen-Wen Chen¹, Zhao-Chong Zeng¹, Zuo-Lin Xiang²

¹Zhongshan Hospital of Fudan University, China,

²Shanghai East Hospital, Tongji University School of Medicine, China

Background: Bone metastasis (BM) has long been recognized as a major threat to the quality of life of hepatocellular cancer (HCC) patients. While LncRNA34a (Lnc34a) has been shown to regulate colon cancer stem cell asymmetric division, its effect on HCC BM remains unknown. **Methods:** In situ hybridization and quantitative real-time polymerase chain reaction (qRT-PCR) were used to detect the expression of Lnc34a in HCC tissues and cell lines. Ventricle injection model was constructed to explore the effect of Lnc34a on BM in vivo. The methylation of miR-34a promoter and histones deacetylation were examined by using bisulfate-sequencing PCR and chromatin immunoprecipitation assays. RNA pull down and RNA immunoprecipitation were performed to the interaction between Lnc34a and epigenetic regulators. Dual-luciferase reporter assay was conducted to find miR-34a target. The involvement of TGF- β pathway in the BM from HCC was determined by qRT-PCR, western, and Elisa assays. **Results:** We found that Lnc34a was significantly overexpressed in HCC tissues and associated with BM. Both in vitro and in vivo experiments indicate that the restoration or knockdown of Lnc34a expression in HCC cells had a marked effect on cellular migration, invasion, and metastasis. Mechanistic analyses suggested that Lnc34a epigenetically suppresses miR-34a expression through recruiting DNMT3a via PHB2 to methylate miR-34a promoter and HDAC1 to promote histones deacetylation. On the other hand, miR-34a targets Smad4 via the TGF- β pathway, followed by altering the transcription of the downstream genes (i.e., CTGF and IL-11) that are associated with BM. **Conclusions:** Our study is the first to document the pro-bone metastatic role of Lnc34a in BM of HCC and reveal a novel mechanism for the activation of the TGF- β signaling pathway in HCC BM, providing evidence of a potential therapeutic strategy in HCC BM.

O-005

Post-Treatment Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios as Prognostic Factors for Small Hepatocellular Carcinoma Patients Treated with Stereotactic Body Radiation Therapy

Yuan Zhuang¹, Yixing Chen¹, Baoying Yuan¹, Zhaochong Zeng¹

¹Department of Radiation Oncology, Zhongshan Hospital, Fudan University, China

Background and Aim: The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory indexes that may reflect immune response to tumors and prognosis. We investigated the independent prognostic values of pre-treatment and post-treatment NLR and PLR and changes in those ratios in patients with small hepatocellular carcinoma (sHCC) treated with stereotactic body radiation therapy (SBRT). **Methods:** We retrospectively reviewed 60 sHCC patients who received SBRT from November 2012 to February 2017. NLR and PLR were calculated by division of neutrophil and platelet counts, respectively, by lymphocyte counts. Independent factors for progression-free survival (PFS) and overall survival (OS) were determined by the Kaplan-Meier method, log-rank test, and Cox multivariate regression. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were also calculated. **Results:** The median follow-up was 36.9 (range: 4.1–73.5) months. Median PFS was 21.4 (range: 1.8–66.9) months. The 1-year and 2-year PFS rates were 76.7% and 55.0%, respectively. The 1-year and 2-year OS rates were 95.0% and 78.3%, respectively. In multivariate analysis, post-treatment NLR ≥ 6.5 and PLR ≥ 263.0 indicated poor PFS (HR: 3.45; 95% CI: 1.53–9.82 and HR: 4.46; 95% CI: 1.56–10.04, respectively) and poor OS (HR: 2.17; 95% CI: 1.01–8.05 and HR: 3.63; 95% CI: 0.95–8.01, respectively). Post-treatment increase in NLR ≥ 2.7 -fold was also a negative independent predictor of poor OS ($p < 0.05$). However, pre-treatment NLR and PLR exhibited no significant association with patient's outcome ($p > 0.05$). **Conclusions:** High post-treatment NLR and PLR and change in NLR ≥ 2.7 -fold were associated with poor PFS and OS in patients treated with SBRT and should be considered reliable and independent prognostic biomarkers for patients with sHCC.

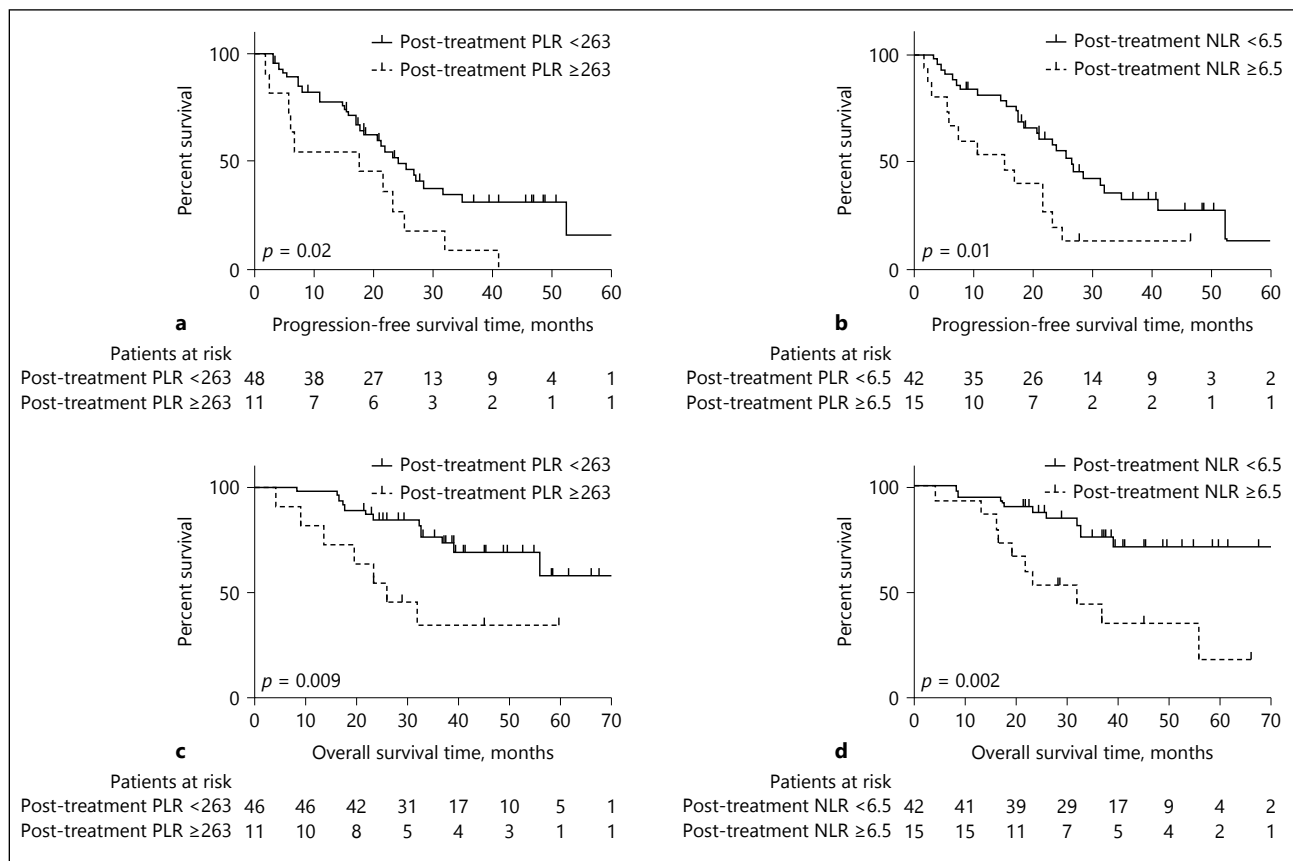


Fig. 1. (for Abstract no O-005).

O-006

Increased Frequency of PD-1+CD57+Siglec-7- Dysfunctional NK Cells in Patients with Non-Alcoholic Fatty Liver Disease

Yuzuru Sakamoto^{1,2}, Sachiyo Yoshio², Akihisa Nagatsu¹, Yoh Asahi¹, Shingo Shimada¹, Tatsuya Orimo¹, Hirofumi Kamachi¹, Toshiya Kamiyama¹, Tatsuya Kanto², Akinobu Taketomi¹

¹Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Japan,

²National Center for Global Health and Medicine, The Research Center for Hepatitis and Immunology, Japan

Background and Aims: The proportion of non-alcoholic fatty liver disease (NAFLD) has been increasing as a cause of hepatocellular carcinoma (HCC) worldwide. Natural killer (NK) cells are involved in the first line of immune defense against cancer. NK cell function is regulated by activating and inhibitory NK cell receptors. However, the role of NK cells in the pathogenesis of NAFLD and NAFLD-HCC is still largely unknown. In this study, we aimed to clarify the phenotypic and functional features of NK cells in NAFLD patients. **Methods:** We performed mass cytometry (CyTOF) and flow

cytometry analysis of NK cells in 35 NAFLD patients (22 chronic hepatitis (CH), 8 liver cirrhosis (LC), 5 with HCC (HCC)) and 11 healthy donors (HDs). We also measured NK cell function in the presence of IL-12 and IL-18. **Results:** The frequency of NK cells was lower in NAFLD patients compared to HDs. PD-1, CD57, ILT2 were highly expressed, and Siglec-7, NKp30, NKp46 were downregulated on NK cells from NAFLD patients, compared with those of HDs. In NAFLD patients, Siglec-7 levels on NK cells were negatively correlated with PD-1 and CD57, and positively correlated with NKp30 and NKp46. The other inhibitory markers (NKG2A, KIR3DL1 and KIR2DL2/L3), activating markers (CD69 and NKG2D) and checkpoint markers (Tim-3 and TIGIT) were comparable between NAFLD patients and HDs. Siglec-7 expression levels on NK cells were significantly downregulated in NAFLD-HCC patients than those in NAFLD patients. The IFN γ production and CD107a expression on NK cells were also decreased in NAFLD patients. PD-1+CD57+Siglec-7- NK cells were observed in NAFLD patients, rarely in HDs. PD-1+CD57+Siglec-7- NK cells were functionally impaired compared to other NK subsets. **Conclusions:** In patients with NAFLD, NK cells are reduced and functionally impaired, the reason of which may be the increased proportion of dysfunctional PD-1+ CD57+ Siglec-7- NK subset.

O-007

Association Between Tumor Response by mRECIST and Overall Survival in Patients with Poorly Differentiated Hepatocellular Carcinoma (HCC) in REFLECT Study

Masatoshi Kudo¹, Kazuomi Ueshima¹, Hiroshi Aikata², Toshiyuki Tamai³, Kenichi Saito³, Kenji Ikeda⁴

¹Kindai University Faculty of Medicine, Osaka, Japan;

²Hiroshima University Hospital, Hiroshima, Japan, Japan; ³Eisai Co., Ltd., Tokyo, Japan; ⁴Toranomon Hospital, Tokyo.

Background: Lenvatinib (LEN) demonstrated a treatment effect on overall survival (OS) compared to sorafenib (SOR), statistically confirmed by non-inferiority in REFLECT. Objective response rates (ORR) were superior with LEN vs SOR. Recently, objective response (OR) by mRECIST was shown to be an independent predictor of OS in REFLECT regardless of treatment. HCC with poor histological subtype was reported to show aggressive phenotype such as worse prognosis. Here, we report a post-hoc exploratory analysis on the association between treatment efficacy and overall survival in patients (pts) with poorly differentiated HCC in REFLECT. **Methods:** OR assessed by investigators per mRECIST were used to analyze the association between OR and the survival time of pts treated with LEN or SOR. The OS of responders (CR or PR) was compared to that of non-responders (SD, PD, or UNK/NE) irrespective of treatment with Kaplan-Meier method. Baseline patients' characteristics of responders were compared to those of non-responders. **Results:** Of 954 pts enrolled in REFLECT, pathological information were recorded in 323 pts. Forty-two pts had been given to diagnosis of poorly differentiated HCC. The median time from biopsy for pathology assessment to study enrollment of those pts was 3.2 months (mons). In poorly differentiated HCC, mOS was 40.1 mons for responders (n = 13) and 8.4 mons for non-responders (n = 29), (HR [95% CI]: 0.25 [0.09, 0.66], Mantel-Byar Test: P-value: 0.003) in pts with this histological subtype. Responders were more observed in pts with baseline Child-Pugh (CP) score 5 compared to CP score 6 and in pts in LEN arm compared to those in SOR arm. **Conclusions:** This exploratory analysis suggests that that OR may be an

independent prognosis factor of OS also in poorly differentiated HCC, while sample size is small. Further studies would be warranted.

Diagnosis and Liver Imaging / Epidemiology and Surveillance / Miscellaneous

O-008

Pre-Operative Staging Migration Between Dynamic CT and Gd-EOB-MRI is a Prognostic Factor in Patients with HCCs

Chih-Horng Wu¹, Po-Chin Liang¹, Yu-Hsin Lee¹, Ming-Chih Ho¹

¹National Taiwan University Hospital, Taiwan

Background and aim To investigate whether staging migration between dynamic CT and Gd-EOB-MRI is a prognostic factor in HCC patients received liver section. **Materials and methods** This is a retrospective, comparative, non-randomization study. From 2014 Jan to 2017 Dec, patients with HCCs received liver resection were enrolled. The inclusion criteria were patients received both dynamic CT and Gd-EOB-MRI imagings within one month before operation. The tumor staging were assessed by dynamic CT (cAJCC) and Gd-EOB-MRI (mAJCC). Difference between cAJCC and mAJCC was defined as stage migration. The clinical, imaging, pathologic factors and survival were compared between patients with/without staging migration. **Results** Total 120 patients were included. 10 patients had T1a, 90 patients had T1b, 11 patients had T2, 8 patients had T3 and one patient had T4 cAJCC T stage by CT scan. 7 patients had T1a, 73 patients had T1b, 32 patients had T2, 7 patients had T3 and one patient had T4 mAJCC T stage by Gd-EOB-MRI. The percentage of staging migration was 20.8% (Table 1). The staging migration happened in cAJCC T1a to T2 lesion and no staging migration was observed in cAJCC T3 and T4 lesions. There were signif-

Table 1. Staging Migration (25/120: 20.8%) (for Abstract no O-008)

	CT T1a	CT T1b	CT T2	CT T3	CT T4
EOB T1a	7	0	0	0	0
EOB T1b	1	71	1	0	0
EOB T2	1	15	8	0	0
EOB T3	1	4	2	8	0
EOB T4	0	0	0	0	1
Staging Migration	3/10 (30.0%)	19/90 (21.1%)	3/11 (27.3%)	0/8 (0.0%)	0/1 (0.0%)

icant difference in AFP and disease free survival between patients with/without staging migration in cAJCC T1a to T2 stages. Conclusion Staging migration between dynamic CT and Gd-EOB-MRI served as a prognostic factor in patients with T1a to T2 lesion evaluated by dynamic CT.

O-009

Liver Imaging Reporting and Data System Category 3 and 4 Observations: Categorization Pathway as an Indicator of Risk of Progression

Yeun-Yoon Kim^{1,2}, Jin-Young Choi², Myeong-Jin Kim²

¹Samsung Medical Center, Korea, ²Severance Hospital, Korea

Background/Aim: To investigate the risk of progression in Liver Imaging Reporting and Data System (LI-RADS) category 3 (LR-3) and 4 observations according to categorization pathway. **Methods:** Among 277 treatment-naïve patients with indeterminate focal liver lesions on gadolinium-enhanced MRI from 2014 to 2015 and chronic hepatitis B or liver cirrhosis, we recruited 84 patients who received histopathological confirmation of lesion or had at least one follow-up CT or MRI before locoregional treatment. A total of 113 observations were retrospectively categorized with LI-RADS v2018, and the element among LI-RADS diagnostic table, ancillary features, and tie-breaking rules which contributes to

categorization (i.e., categorization pathway) was identified. Pathology results and follow-up data were summarized according to the categorization pathway at baseline. Cumulative incidence curves for progression to malignancy (pathologic diagnosis or malignant LI-RADS category) were generated for each categorization pathway and compared using log-rank tests with a resampling extension. **Results:** Of 51 LR-3 and 62 LR-4 observations, pathways were determined by LI-RADS diagnostic table in 47 (92.2%) and 15 (24.2%), ancillary features in 4 (7.8%) and 40 (64.5%), and tie-breaking rules in 0 and 7 (11.3%) observations, respectively. The cumulative incidence of progression to malignancy was higher for LR-4 observations than for LR-3 observations (66.4% vs. 16.4% at 2 years; $P < 0.001$). Hypervascular LR-4 observations had a higher cumulative incidence of progression to malignancy than other LR-4 or hypervascular LR-3 observations (100% vs. 40.3% at 1 year; $P = 0.042$), which had, in turn, a higher cumulative incidence than downgraded or hypovascular LR-3 observations (40.3% vs. 5.6% at 1 year; $P = 0.003$). **Conclusion:** The risk of progression can be stratified by several categorization pathways in LR-3 and LR-4 observations. Categorization pathways may be useful to suggest the risk of progression in indeterminate observations.

O-010

Effectiveness and Feasibility of External Beam Radiotherapy for Hepatocellular Carcinoma with Inferior Vena Cava and/or Right Atrium Involvement: A Multicenter Trial in Korea (KROG 17-10)

Chai Hong Rim¹, Bae-Kwon Jeong², Tae Hyun Kim³, Jin Hee Kim⁴, Hyun-Cheol Kang⁵, Jinsil Seong⁶

¹Korea University Medical College, Korea, ²Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Korea, ³National Cancer Center, Korea, ⁴Keimyung University School of Medicine, Korea, ⁵Seoul National University Hospital, Seoul National University College of Medicine, Korea, ⁶Yonsei Cancer Center, Korea

Background and Purpose: Hepatocellular carcinoma (HCC) involving the inferior vena cava (IVC) and/or right atrium (RA) can affect systemic circulation, causing fatal complications. Standard treatment is yet to be established due to its rarity and intractability. We sought to determine the clinical efficacy of external beam radiotherapy (EBRT) in HCC treatment. **Materials and Methods:** Our group designed this multicenter trial and recruited patients with HCC and IVC and/or RA involvement. Forty-nine patients from six institutions received EBRT with median dose of 46.7 (range: 35.4–71.5) Gy during 2009–2016. The primary outcome was overall survival (OS), and relevant predictors were evaluated. **Results:** Median follow-up length was 9.3 (range: 1.1–119) months.

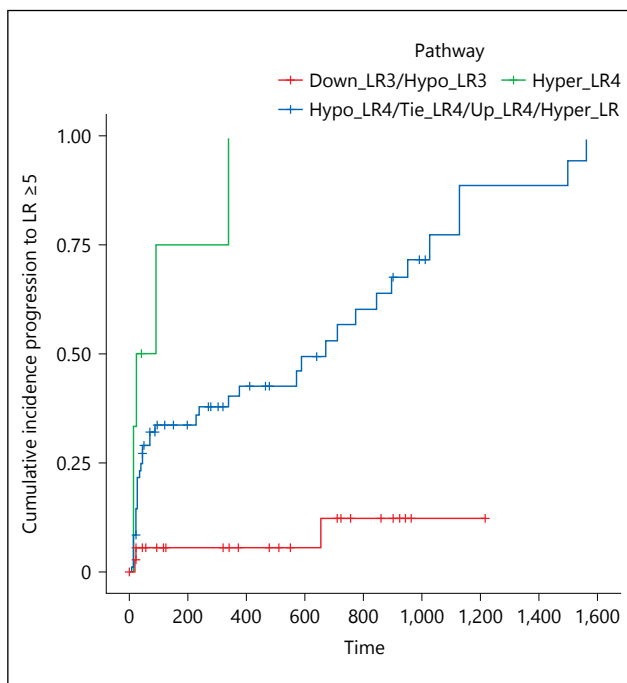


Fig. 1. (for Abstract no O-009).

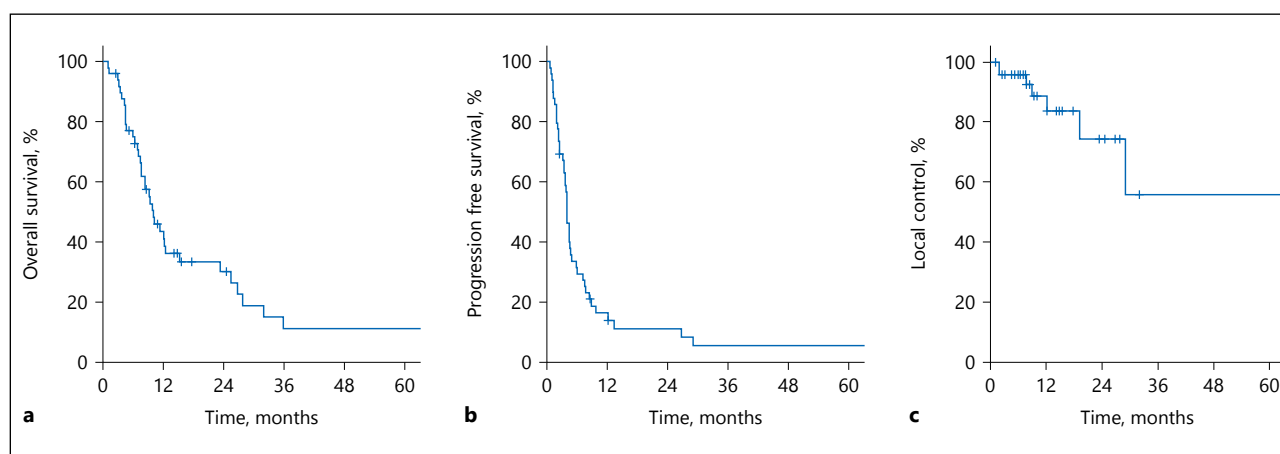


Fig. 1. (for Abstract no O-010).

Median survival, 1-, and 2- year OS rates were 10.1 months (95% confidence interval [CI]: 7.5–12.7 months), 43.5%, and 30.1%, respectively. Significant factors affecting OS were alpha-fetoprotein level ≥ 300 ng/mL (risk ratio [RR]: 2.34, $p = 0.025$), tumor multiplicity (RR: 2.56, $p = 0.028$), and patient volume of institutions (high- vs. middle volume centers) (RR: 3.58, $p = 0.001$). Local control rates were 88.7% and 74.5% at 1 and 2 years, respectively. The most common first failure site was the lung (21/49, 42.9%) followed by liver outside the EBRT field (17/49, 34.7%). One case of possible radiation-induced liver disease was noted, with transient alkaline phosphatase elevation. **Conclusion:** EBRT can yield favorable local control in HCC with IVC and/or RA involvement. Systemic treatment may be more indicated as factors reflecting tumor aggressiveness were significant, and first distant failure is common.

O-011

Viscoelasticity Measurement in Patients with Nonalcoholic Fatty Liver Disease Using Shear Wave US Elastography

Katsutoshi Sugimoto¹, Masakazu Abe¹, Yu Yoshimasu¹, Hirohito Takeuchi¹, Yoshitaka Kasai¹, Takao Itoi¹

¹Department of Gastroenterology and Hepatology, Tokyo Medical University, Japan

Aim: To investigate the usefulness of shear wave (SW) speed (related to viscoelasticity), dispersion slope (related to viscosity) and attenuation value (related to degree of steatosis) obtained using a new ultrasound (US) elastography system in patients with histologically confirmed nonalcoholic fatty liver disease (NAFLD). **Methods:** US-based SW imaging system (Aplio i800; Canon Medical Systems) was used to measure three US parameters such as SW speed (m/s), dispersion

slope ([m/s]/kHz) and attenuation value (dB/cm/MHz) and compare to liver histopathology such as fibrosis, ballooning, lobular inflammation, and steatosis as assessed by NAFLD Activity Score in 24 patients diagnosed with NAFLD. **Results:** In univariate analysis, SW speed was significantly correlated with fibrosis (Spearman's rank correlation coefficient: $\tilde{r} = 0.77$; $P < 0.01$) and ballooning ($\tilde{r} = 0.59$; $\tilde{N} < 0.01$), respectively. Dispersion slope was significantly correlated with lobular inflammation ($\tilde{r} = 0.58$; $\tilde{N} < 0.01$), ballooning ($\tilde{r} = 0.53$; $\tilde{N} < 0.01$), and fibrosis ($\tilde{r} = 0.46$; $\tilde{N} = 0.02$), respectively. Attenuation value was significantly correlated with steatosis ($\tilde{r} = 0.71$; $\tilde{N} < 0.01$). In multivariable analysis with histologic features as independent variables, SW speed was significantly related to fibrosis ($\tilde{N} < 0.05$). Dispersion slope was significantly related to lobular inflammation ($\tilde{N} < 0.05$). However, attenuation value was not significantly correlated with steatosis ($\tilde{N} = 0.07$). **Conclusion:** SW speed is more useful than dispersion slope for predicting the degree of fibrosis, and dispersion slope is more useful than SW speed for predicting the degree of necroinflammation. Dispersion slope, which reflects viscosity, may provide additional pathophysiological insight into NAFLD.

O-012

Assessment of Preoperative Liver Function in Patients with Hepatocellular Carcinoma

Takashi Kokudo¹, Chikara Shirata¹, Meguri Tanimoto¹, Junichi Arita¹, Junichi Kaneko¹, Nobuhisa Akamatsu¹, Takeaki Ishizawa¹, Kiyoshi Hasegawa¹

¹The University of Tokyo, Japan

Background/Aim: Precise preoperative evaluation of the patient's liver function is essential for surgical decision making in patients with hepatocellular carcinoma (HCC). The aim of the study is to improve the predictive power of indo-

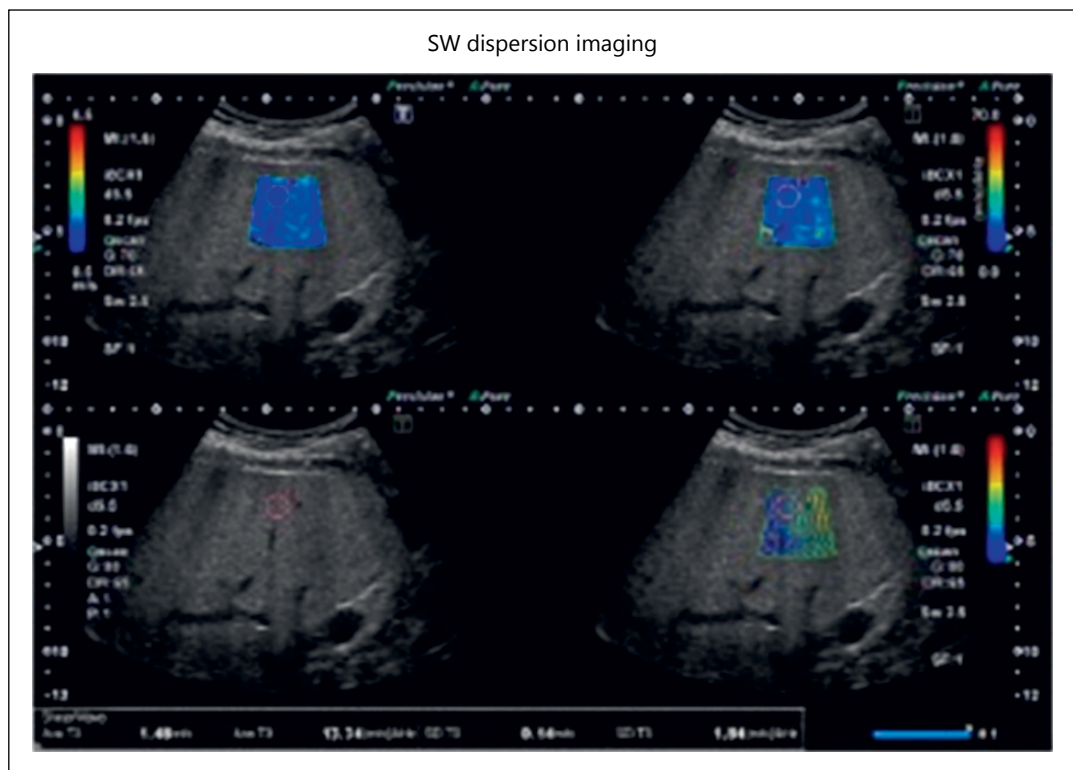


Fig. 1. (for Abstract no O-011).

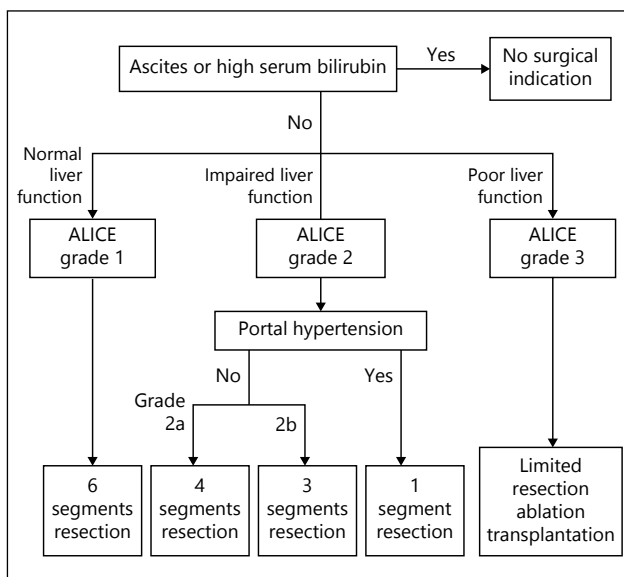


Fig. 1. Surgical treatment strategy for HCC according to the ALICE grade and PH (for Abstract no O-012).

cyanine green retention rate at 15 minutes (ICG R15).

Methods: The Albumin-Indocyanine Green Evaluation (ALICE) grading system, incorporating only serum albumin level and ICG R15, was developed based on the overall survival

of 1868 HCC patients: linear predictor = $0.663 \times \log_{10} \text{ICG R15} (\%) - 0.0718 \times \text{albumin (g/L)}$ (cut-off value: -2.20 and -1.39). We analyzed the predictive power for the postoperative short-term outcome after liver resection in 1025 patients with HCC. Furthermore, in order to clarify ICG excretory defect, immunohistochemistry analysis of the normal liver tissue was performed for OATP1B3 in ten patients where ICG R15 values were over 40%. **Results:** Determination of the ALICE grade allowed better prediction of the risk of postoperative liver failure than the previously reported model based on the presence/absence of portal hypertension (PH). A combination of ALICE grade and PH further predicted the risk of postoperative liver failure. In patients with high ICG R15 values, six patients showed absence of OATP1B3 and all these patients showed normal liver function by 9mTc-GSA hepatic scintigraphy. **Conclusions:** The ALICE grading system is a simple method for prediction of the postoperative short-term outcomes and OATP1B3 measurement may be useful to diagnose ICG excretory defect.

O-013

Potential Benefit of Hepatocellular Carcinoma Surveillance in Patients with Non-Alcoholic Fatty Liver Disease

Yi Qing Tey², Shao Rong John Mok¹,
Wei Rong Benjamin Tay¹, Poh Seng Tan¹,
Wei Chieh Alfred Kow³, Glenn K. Bonney³, Yock Young
Dan^{1,2}, Qingyao Daniel Huang¹

¹Division of Gastroenterology and Hepatology,
National University Health System, Singapore,

²Department of Medicine, Yong Loo Lin School of
Medicine, National University of Singapore, Singapore,

³Division of Hepatobiliary Surgery, National University
Health System, Singapore

Background: Patients with non-alcoholic fatty liver disease (NAFLD) are at risk of developing hepatocellular carcinoma (HCC). We aim to assess the impact of screening for HCC in patients with NAFLD in the Asian cohort. **Methods:** Our retrospective cohort study involved 117 NAFLD patients with HCC diagnosed between January 1, 2007 and December 31, 2017. Assessment of response to treatment was evaluated using mRECIST criteria. The impact of screening was evaluated based on the outcomes of overall survival, response to initial treatment, incidence of recurrence and progression, and time to recurrence and progression. **Results:** Majority of patients did not receive HCC surveillance (82 compared to 35). The surveillance cohort had a higher proportion of cirrhosis than the non-screening group (85.7% compared to 47.6%; $p < 0.001$). Screened patients had significantly smaller tumours (median sum diameter of 2.3 cm, IQR 1.70–4.25 compared to 7.85 cm, IQR 4.23–11.53; $p < 0.001$) with lower AFP (median 6.90 ng/mL, IQR 3.93–31.42 compared to 48.25, IQR 7.78–1064.5; $p = 0.002$) and higher haemoglobin (median 13.2 g/dL, IQR 12.1–13.9 compared to 11.9, IQR 9.9–13.8; $p = 0.014$) levels, and at an earlier BCLC stage ($p < 0.001$). Patients with screening had

longer survival (median 23 months, IQR 13.3–45.5 compared to 13, IQR 3.5–29.0; $p = 0.019$), with a nonsignificant trend towards longer time to progression (median 11.0 months, IQR 7.5–18.5 compared to 5.0, IQR 3–12.3; $p = 0.057$). However, there was no significance difference in progression and recurrence rates between the two groups. **Conclusion:** Hepatocellular carcinoma screening in NAFLD correlates with early identification of HCC with a significant survival benefit.

O-014

Prognoses and Clinicopathological Characteristics of Resected NonBNonC Hepatocellular Carcinoma with High HbA1c

Shingo Shimada¹, Toshiya Kamiyama¹, Tatsuya Orimo¹,
Yuzuru Sakamoto¹, Yo Asahi¹, Akihisa Nagatsu¹,
Hirofumi Kamachi¹, Akinobu Taketomi¹

¹Hokkaido University, Japan

Aim: To investigated the prognoses and clinicopathological characteristics, and postoperative complications of resected hepatocellular carcinoma with high HbA1c. **Methods:** We analyzed 769 patients underwent hepatectomy for HCC between 1997 and 2014. These patients were stratified into the cases with HbA1c ≥ 7.0 (H-A1c: $n = 89$), the cases with HbA1c < 7.0 (L-A1c: $n = 680$). We investigated 1) the prognoses between H-A1c and L-A1c divided by background liver, 2) the clinicopathological characteristics on H-A1c of NonBNonC (NBNC)-HCC, 3) the postoperative complications. **Results:** NBNC were 225 cases, HBV were 304 cases, and HCV were 255 cases. 1) five-year overall survival (OS) rates of all cases, NBNC, HBV, and HCV were 62%, 63%, 61%, and 59%, respectively. As results of the comparison of five-year OS rates between H-A1c and L-A1c, 56% vs. 63% (all cases, $p = 0.10$), 49% vs. 67%

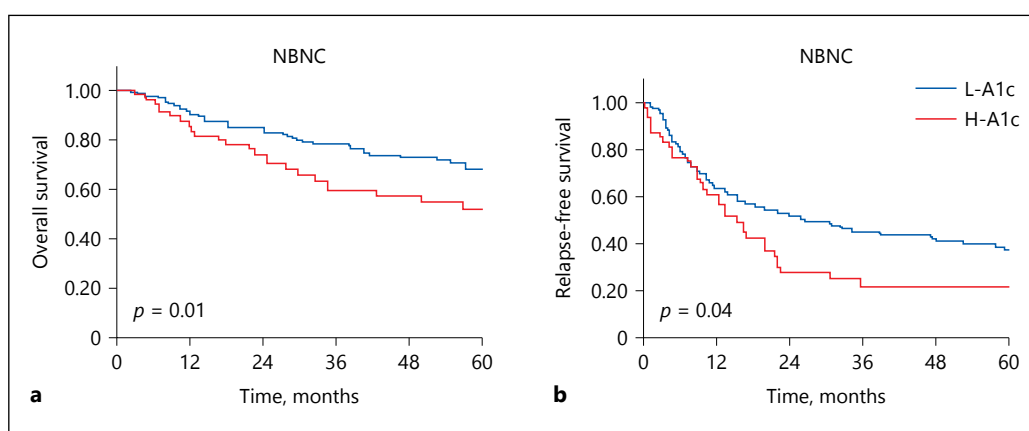


Fig. 1. (for Abstract no O-014).

Table 1. Hepatocellular carcinoma surveillance in patients non-alcoholic fatty liver disease (for Abstract no O-013)**a** Baseline characteristics

	No Screening	Screening	P-Value
Number of patients	82	35	
Age, median (IQR)	71.5 (66–77)	71 (63–76)	0.48
Gender (%)			
Male	59 (72%)	23 (65.7%)	0.500
Female	23 (28%)	13 (34.3%)	
Symptomatic at diagnosis (%)			
Yes	55 (67.9%)	6 (17.6%)	<0.001
No	26 (32.1%)	28 (82.4%)	
Cirrhosis (%)			
Cirrhotic	39 (47.4%)	30 (85.7%)	<0.001
Non-cirrhotic	43 (52.4%)	5 (14.3%)	
Primary nodule size (IQR)			
Median size in cm	7.10 (4.00–10.50)	2.20 (1.65–3.85)	<0.001
Sum diameter of non-multinodular tumors (IQR)			
Size in cm	7.85 (4.23–11.53)	2.30 (1.70–1.25)	<0.001
Vascular invasion (%)			
Yes	17 (21.3%)	2 (5.7%)	0.039
No	63 (78.4%)	33 (94.3%)	
Biochemistry			
Alpha-fetoprotein (ng/mL)	48.25 (7.78–1064.50)	6.90 (3.93–31.42)	0.002
Hemoglobin (g/dL)	11.95 (9.925–13.775)	13.20 (12.075–13.900)	0.014
Alkaline phosphatase (μmol/L)	122.50 (87.00–229.25)	91.50 (69.75–118.25)	0.04
Barcelona clinic liver cancer (BCLC) stage			
0	1 (12%)	9 (26.5%)	<0.001
A	19 (23.5%)	15 (44.1%)	
B	43 (53.1%)	7 (20.6%)	
C	12 (14.8%)	2 (5.9%)	
D	6 (7.4%)	1 (2.9%)	

b Outcomes

	No Screening	Screening	P-Value
SunisaI (IQR)			
Median survival (months)	13 (3.5–29)	23 (13.25–45.50)	0.019
Response after initial treatment (%)			
Complete response	22 (46.8%)	19 (65.5%)	
Partial Response	7 (14.9%)	5 (17.2%)	0.256
Stable Disease	11 (23.4%)	3 (10.3%)	
Progressive Disease	7 (8.5%)	2 (6.9%)	
Recurrence (%)			
Recurrence	12 (48%)	10 (47.6%)	0.736
Non-recurrence	10 (40%)	9 (42.9%)	
Death	3 (12%)	2 (9.5%)	
Time to recurrence (IQR)			
Time to recurrence (months)	9 (5.28)	10.5 (9.49–25)	0.660
Progression (%)			
Progression	27 (61.4%)	15 (50.0%)	0.305
No Progression	9 (20.5%)	11 (36.7%)	
Death	8 (18.2%)	4 (13.3%)	
Time to Progression (IQR)			
Time to progression (months)	5 (3–12.25)	11 (7.5–18.5)	0.057

(NBNC, $p = 0.01$), 59% vs. 62% (HBV, $p = 0.61$), and 38% vs. 61% (HCV, $p = 0.18$). Median relapse free survival (RFS) time were 15 months vs. 20 months (all cases, $p = 0.07$), 15 months vs. 26 months (NBNC, $p = 0.04$), 15 months vs. 15 months (HBV, $p = 0.45$), and 11 months vs. 23 months (HCV, $p = 0.06$). Univariate analyses showed H-A1c had significantly poor prognoses about OS and RFS. However, multivariate analyses showed H-A1c was not a significantly independent factor. 2) H-A1c of NBNC-HCC showed significantly difference about age and platelet, however, liver functions and tumor factors were not different. 3) Regarding the postoperative complications $\geq$ Clavien-Dindo3a, hyperbilirubinemia; 7.9% vs. 3.4% (H-A1c vs. L-A1c; $p = 0.04$), pneumonia; 6.7% vs. 1.6% ($p < 0.01$), and wound infection; 5.6% vs. 0.9% ($p < 0.01$). Median postoperative hospital stay were 17days vs. 16 days ($p = 0.40$). **Conclusions:** High HbA1c alone is not a independent prognostic factor in NBNC-HCC, however, it may somewhat affect the prognoses. High HbA1c can become the risk factor of postoperative complications after hepatectomy.

O-015

Variations in Cancer Stages at Diagnosis and Management Strategies in Hepatocellular Carcinoma (HCC): Data from the HCC Registry in Asia (AHCC08)

Pierce K.H. Chow¹, Lequn Li², Jiangtao Li³, Kiyoshi Hasegawa⁴, Jia Fan⁵, Chien-Hung Chen⁶, Pin-Nan Cheng⁷, Shu-Kui Qin⁸, Nobuyuki Takemura⁹, Poh Seng Tan¹⁰, Tsung-Hui Hu¹¹, Ho-Seong Han¹², Junji Furuse¹³, Edmund Tse¹⁴, Jong Young Choi¹⁵, Young Kim Do¹⁶, Brian K.P. Goh¹⁷, Hee-Jung Wang¹⁸, Jin-Mo Yang¹⁹, Kazuaki Shimada²⁰, Cheng Yuan Peng²¹, Yun Hwan Kim²², Xu Zhu²³, Simone Strasser²⁴, Yuxian Bai²⁵, Yvanka M. Gilliam²⁷, Meenakshisundaram Palaniappan²⁷, Mihir Gandhi²⁸, On behalf of the Asia-Pacific Hepatocellular Carcinoma Trials Group AHCC²⁶

¹National Cancer Centre Singapore, Singapore,

²Guangxi Medical University Cancer Centre, China,

³Second Affiliated Hospital Zhejiang University School of Medicine, China, ⁴The University of Tokyo, Japan, ⁵Zhongshan Hospital, Fudan University, China, ⁶National Taiwan University Hospital, Taiwan, ⁷National Cheng Kung University Hospital, Taiwan, ⁸Nanjing Bai Hospital, China, ⁹National Center for Global Health and Medicine, Japan, ¹⁰National University Hospital, Singapore, ¹¹Kaohsiung Chang Gung Memorial Hospital, Taiwan, ¹²Seoul National University Hospital, Korea, ¹³Kyorin University Faculty of Medicine, Japan, ¹⁴Royal Adelaide Hospital, Australia, ¹⁵Seoul St Mary's Hospital, Korea, ¹⁶Severance Hospital, Yonsei University College of Medicine, Korea, ¹⁷Singapore General Hospital, Singapore, ¹⁸Ajou University Hospital, Korea,

¹⁹St Vincent's Hospital, Korea, ²⁰National Cancer Centre, Japan, ²¹China Medical University Hospital, Taiwan, ²²Korea University Anam Hospital, Korea, ²³Beijing Cancer Hospital, China, ²⁴Royal Prince Alfred Hospital, Australia, ²⁵Harbin Medical University Cancer Hospital, China, ²⁶The Asia-Pacific Hepatocellular Carcinoma Trials Group, Singapore, ²⁷IQVIA Institute, Singapore, ²⁸Singapore Clinical Research Institute, Singapore

Background: While HCC is the 6th most common cancer worldwide, >70% of cases are in Asia. Real-world data on HCC required for sound healthcare policies and marketing strategies are limited. **Methods:** The AHCC08 is a multi-country longitudinal cohort study of patients with HCC diagnosed between 2013 and 2019 (ClinicalTrials.gov: NCT03233360). We performed interim analysis of the presentation and management of the first 951 patients from 25 centres in Australia [AU] (15), China [CN] (565), Japan [JP] (117), Singapore [SG] (106), South Korea [SK] (55) and Taiwan [TW] (93). **Results:** The mode of diagnosis for most patients across the 6 countries was radiological imaging. There is strong association between Hepatitis B status and HCC in China, South Korea, Singapore and Taiwan while in Australia and Japan, it is Hepatitis C. Patients are diagnosed at later stages (Barcelona Clinic Liver Cancer staging) in China. First-line treatment for early stage (Stage 0 and Stage A) patients were liver resection (0% AU; 80% CN; 79% JP; 35% SG; 74% SK; 37% TW), radiofrequency ablations (57% AU; 4% CN; 11% JP; 13% SG; 4% SK; 51% TW) and TACE (29% AU; 13% CN; 8% JP; 11% SG; 13% SK; 2% TW). For intermediate (Stage B) patients, in Australia, China and South Korea (~50% aggregated) TACE was preferred first-line treatment followed by liver resection while 26% of patients in Singapore were treated with SIRT in this setting. In Singapore, South Korea and Taiwan, systemic therapy was carried out as the first-line therapy for advanced (Stage C) patients, followed by TACE. 8% of stage C and 60% of stage D patients received best supportive care. Stage D patients were underrepresented in this registry. **Conclusions:** There is considerable variation in stage at presentation, aetiology and management patterns of HCC among 6 countries.

O-016

Comparison of EASL 2018 and LI-RADS 2018 for the Noninvasive Diagnosis of Hepatocellular Carcinoma Using MRI

Sunyoung Lee¹, Myeong-Jin Kim¹

¹Severance Hospital, Yonsei University College of Medicine, Korea

Background/Aim: Hepatocellular carcinoma (HCC) is the only malignancy where standard practice for diagnosis is to use imaging without pathological confirmation in high-

risk patients; thus, reliable noninvasive imaging criteria are crucial. We compared the diagnostic performances of the European Association for the Study of the Liver (EASL) 2018 and Liver Imaging Reporting and Data System (LI-RADS) 2018 criteria on magnetic resonance imaging (MRI) for the noninvasive diagnosis of HCC in high-risk patients. **Methods:** This retrospective study included 382 lesions (286 HCCs, 63 benign lesions, and 33 other malignancies) at high risk of HCC who underwent preoperative multiphase contrast-enhanced MRI between January 2015 and December 2016. Two readers independently assessed all observations according to the EASL 2018 and LI-RADS 2018 criteria, and the per-observation diagnostic performances were compared using the generalized estimating equation method. **Results:** The percentages of HCC were for each LI-RADS category were 97.6% for LR-5, 61.2% for LR-4, 14.3% for LR-3, 0% for LR-2, 100% for LR-TIV, and 55.6% for LR-M. LR-5 category of LI-RADS 2018 showed slightly higher sensitivity (72.4% vs. 69.2%) and specificity (94.8% vs. 91.7%) than EASL 2018 for the diagnosis of HCC, but the difference was not statistically significant (all, $P > 0.05$). On combining the LR-5 and LR-4 categories, LI-RADS 2018 had a higher sensitivity (86.7% vs. 69.2%) but a lower specificity (67.7 vs. 91.7%) than EASL 2018 (all, $P < 0.01$). **Conclusion:** EASL 2018 and LR-5 category of LI-RADS 2018 showed comparable sensitivity and specificity for the diagnosis of HCC. The combination of LR-5 and LR-4 categories of LI-RADS 2018 had a higher sensitivity, but its specificity was significantly lower.

Treatment: Surgical Resection and Transplantation

O-017

Clinicopathological Characteristics of Non-B Non-C Hepatocellular Carcinoma (NBNC-HCC) Underwent Liver Resection

Tomokazu Kusano¹, Takeshi Aoki¹, Tatsuya Yamazaki¹, Takahito Hirai¹, Koudai Tomioka¹, Tomoki Hakozaiki¹, Yusuke Wada¹, Nogaki Kouji¹, Tomotake Koizumi¹, Akira Fujimori¹, Masahiko Murakami¹

¹Showa University School of Medicine, Japan

Background: The number of patients with NBNC-HCC has increased recently. The characteristics of NBNC-HCC remain unclear. The purpose of the present study was to investigate the clinical characteristics and prognoses of NBNC-HCC. **Materials and Methods:** 58 patients with NBNC-HCC (Group N), 30 patients with HBV (Group B), and 70 patients with HCV (Group C) who underwent liver resection were analyzed retrospec-

tively. **Results:** Cause of NBNC-HCC were alcohol (46.6%), diabetes mellitus (18.9%), autoimmune disease (8.6%), NASH (3.4%). The age was higher in Group N (71.3 y) than those in Group B (65.3 y) or Group C (70.6 y). The percentage of men were significantly higher in Group N (82.8%) than those in Group C (64.3%). Though there was not significant difference, the hepatic functional reserve was better in Group N than that in Group B or C. Tumor size was significantly largest in Group N (48.9 mm) and Group B (49.8 mm) than those in Group C (34.8 mm). As for this review by the cause, NBNC-HCC caused by diabetes mellitus was largest tumor (61.2 mm). The percentage of patients who had liver cirrhosis was significantly lower in Group N (13.8%) than that in Group B (50.0%) or Group C (45.8%). The poorly-differentiated rate was lower in Group N (5.1%) than that in Group B (35.7%) or Group C (27.1%). The recurrence rate was lower in Group N (39.7%) than that in Group B (64.3%) or Group C (56.3%). **Conclusions:** Though most of patients with NBNC-HCC appears to be detected at the large tumor, such patients have a good liver function and prognosis. It was suggested that the improvement of lifestyle and the educational measures for NBNC-HCC were important to detect at early stage.

O-018

Ten Year Survivors After Hepatocellular Cancer

Linda L. Wong^{1,3}, Tomoki Sempokuya², Eric A. Wien², Jeffrey Pan², Sandi A. Kwee³

¹Dept of Surgery, University of Hawaii, USA, ²Dept of Medicine, University of Hawaii, USA, ³Cancer Center, University of Hawaii, USA

Background: Long-term survival after hepatocellular cancer (HCC) is difficult to achieve due to recurrence in the setting of chronic liver disease. We sought to identify factors that were predictive of 10-year survival after the diagnosis of HCC. **Methods:** In a prospectively-collected database of 1374 HCC cases (1993–2019), 575 patients had at least 10 years of follow up and 70 (7%) survived 10 years. These 70 patients were compared to 164 patients in the cohort who had liver resection or transplant and died before 10 years. Data compared: demographics, tumor characteristics, treatment, recurrence and treatment of recurrence. **Results:** Ten-year survivors were younger and had smaller tumor size and lower alpha fetoprotein, AST, ALT, platelets and neutrophil/platelet ratio compared to non 10-year survivors. Univariate analysis showed that 10-year survivors were less likely 65 years or older or to have diabetes, hypertension or tumors at least 5 cm. Multivariate analysis showed only age and diabetes to be predictive. Of the 10-year survivors, 36 underwent transplant, 27 had liver resection and 7 patients had locoregional therapy. Of the 10-year survivors, recurrence occurred in 24 patients (34.3%) with mean time to recurrence 1712 (SD1277) days and 23

Table 1. (for Abstract no O-018)

	10 yr survivors (n = 70)	10 yr nonsurvivors (n = 168)	p value
Age (years)	55.5±7.5	62.2±11.0	<0.001
Mean tumor size (cm)	4.0±2.4	6.7±4.68	<0.001
Alpha-fetoprotein	2,479±14,355	13,787±81,011	0.049
AST	64.3±45.5	73.6±58.9	0.03
ALT	60.5±38.5	64.0±52.4	0.03
Platelets (×10 ³ /cc)	149.6±77.3	190.5±101.2	0.03
Neutrophil/Platelet ratio	2.33±1.88	4.20±3.50	0.002
Mean survival (days)	5,071±983 days	1,107±76 days	<0.001

(96%) patients had treatment for recurrence. In 164 non 10-year survivors, 136 had liver resection and 28 had transplant. Recurrence occurred in 80 non 10-year survivors (48.7%) with mean time to recurrence of 460 (SD444.0) days and 61 (76.3%) patients had treatment of the recurrence. Recurrence rate was 23.4% after transplant, 50.9% after resection and 85.7% after just locoregional therapy. **Conclusions:** Long-term survivors mostly occur after resection or transplant, but 10% of our cohort survived 10 years with only locoregional therapy. Recurrence of HCC occurs in both 10-year survivors and non-survivors, but later recurrence with aggressive treatment of the recurrence may allow for 10-year survival.

patients was within Milan criteria in PLT, and 36.7% of patients was within Milan criteria in SLT. 10 patients developed HCC recurrence. 5/10 patients underwent surgical resection of metastasis and are alive without re-recurrence. 1/10 patient underwent lung resection but developed re-recurrence, and has been on systemic chemotherapy. Other 4 patients died from HCC recurrence. 1 yr-, 3 yr-, 5 yr- recurrence-free-survival of PLT group were 92.7%, 87.5%, and 87.5%, while those of SLT group were 72.7%, 63.6%, and 63.6% (P = 0.010). 1 yr-, 3 yr-, 5 yr- Overall-survival of PLT group were 97.6%, 92.3%, and 92.3%, whereas those of SLT group were 100%, 90.9%, and 79.6% (P = 0.319). **Conclusion:** SLT for HCC showed higher incidence of recurrence, however, overall survival was not inferior. SLT could be one of the treatment option.

O-019

Salvage Living Donor Liver Transplantation for Hepatocellular Carcinoma: A Single-Center Experience

Norio Kawamura¹, Ryoichi Goto², Masaaki Watanabe¹, Yoshikazu Ganchiku², Toshiya Kamiyama², Tsuyoshi Shimamura³, Akinobu Taketomi^{1,2}

¹Department of Transplant Surgery, Hokkaido University Graduate School of Medicine, Japan,

²Gastroenterological Surgery 1, Hokkaido University Hospital, Japan, ³Division of Organ Transplantation, Hokkaido University Hospital, Japan

Background: Due to the shortage of deceased liver donor, salvage living donor liver transplantation (SLT) for hepatocellular carcinoma (HCC) has been performed in Japan. However, the significance of SLT has been controversial. **Aim:** To evaluate the outcome of salvage living donor liver transplantation for HCC. **Material and Methods:** This is a retrospective chart review study. Living donor liver transplantation performed in our institute were included in this study. Patients died within 6 months were excluded from the study. **Results:** During study period, 53 liver transplantation for HCC were performed. 79.2%(42/53) were primary liver transplantation (PLT) and 20.8%(11/53) were SLT. 66.7% of

O-020

Laparoscopic Resection of the HCC above the Hepatic Hilum Using Color ICG Fluorescence System

Yasuji Seyama¹, Masaru Matsumura¹, Satoshi Nemoto¹, Jun Muto¹, Yusuke Ome¹, Jun Imamura²

¹Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan, ²Department of Hepatology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Japan

Background/Aim: The ICG fluorescence method is applied to the operation for hepatocellular carcinoma (HCC), especially in laparoscopic liver resection. Recently, we have been able to use color ICG fluorescence method by superimposing fluorescence image on a high vision images. On the other, it is sometimes difficult to detach the tumor from hepatic hilum, because the border is not clear by macroscopic appearance. Here we show two cases with HCC above the hepatic hilum, and examined the advantages and cautions of ICG fluorescence method. **Methods:** We experienced two

cases of HCC in segment 4 just above the hepatic hilum. In both cases, tumor was solitary and the size was 2 cm in diameter. The day before surgery, 2.5 mg of ICG was intravenously administered to the patients. We used color ICG fluorescence system (PINPOINT, Stryker) during the operations to identify the tumor. **Results:** In both cases, we could identify the tumor by ICG fluorescence. We were able to detach the tumors from the hepatic hilum while looking at tumor fluorescence. In case 1, the tumor fluoresced more than the macroscopic border, then we extended the resection area according to the images. In case 2, the tumor fluoresced less than the macroscopic border, and half of the tumor did not fluoresce. We resected the tumor according to both the macroscopic appearance and ICG fluoresce. We could complete the planned operations. **Conclusion:** ICG fluoresce is useful for resect the tumors above the hepatic hilum, but care must be taken as tumor fluorescence is different.

O-021**Algorithm for Resecting Hepatocellular Carcinoma in the Caudate Lobe***Yutaka Midorikawa¹, Tadatoshi Takayama¹*¹Nihon University School of Medicine, Japan

Background/Aim: Owing to a deep location, resection of HCC originating in the caudate lobe is challenging, but a plausible guideline enabling safe, curable resection remains unknown. The aim of this study is to propose an algorithm for resecting hepatocellular carcinoma (HCC) in the caudate lobe. **Methods:** We developed an algorithm based on sublocation or size of the tumor and liver function to guide the optimal procedure for resecting HCC in the caudate lobe, consisting of 3 portions (Spiegel, process, and caval). Partial resection was prioritized to remove Spiegel or process HCC, while total resection was aimed to remove caval HCC depending on liver function. **Results:** According to the algorithm, we performed total (n = 43) or partial (n = 158) resections of the caudate lobe for HCC in 174 of 201 patients (compliance rate, 86.6%), with a median blood loss of 400 (10–4530) mL. Postoperative morbidity (Clavien grade $\geq$ IIIb) and mortality rates were 3.0% and 0%, respectively. After a median follow-up of 2.6 years (range, 0.5–14.3), the 5-year overall and recurrence-free survival rates were 57.3% and 15.3%, respectively. Total and partial resection showed no significant difference in overall survival (71.2% vs 54.0% at 5 yr; $P = 0.213$), but a significant factor in survival was surgical margin (58.0% vs 45.6%, $P = 0.034$). The major determinant for survival was vascular invasion (hazard ratio 1.7, 95% CI 1.0–3.1, $P = 0.026$). **Conclusions:** Our algorithm-oriented strategy is appropriate for the resection of HCC originating in the caudate lobe because of the acceptable surgical safety and curability.

O-022**Result of Volume Reduction Hepatectomy for Highly Advanced Hepatocellular Carcinoma***Yoh Asahi¹, Toshiya Kamiyama¹, Tatsuya Orimo¹, Shingo Shimada¹, Akihisa Nagatsu¹, Hirofumi Kamachi¹, Akinobu Taketomi¹*¹Hokkaido University Hospital, Japan

Background/Aim: Role of volume reduction hepatectomy in highly advanced hepatocellular carcinoma (HCC) is not established yet. The aim of this report is to examine the clinical effect of volume reduction hepatectomy in highly advanced HCC. **Method:** Clinical data from 30 unresectable HCC patients, who underwent volume reduction hepatectomy at our department after January 2000 were retrospectively reviewed. The median survival time (MST) and survival rates after the hepatectomy was examined in All (all patients), Group.1 (patients who achieved complete remission by multidisciplinary treatment) and Group.2 (patients who did not achieve complete remission). **Result:** There was 28 male and 2 female, with their mean age 62.8 ± 11.4 years (44–89). All the patients had multiple tumors and average diameter of the largest tumor was 9.5 ± 4.8 cm (1–19.5). The classifications of differentiation of HCCs were well in 1 patient, mod in 16 patients and por in 13 patients. After the volume reduction hepatectomy, 29 patients had residual tumors in remnant liver. Three patients had extra-hepatic metastasis. Seventeen patients had macrovascular invasion. The average serum level of AFP was 3084.8 ± 8028.6 and PIVKA2 was 51542.3 ± 125666.8 . The complete remission was achieved in 8 patients by multidisciplinary treatment. The MST and survival rates at 1, 3 and 5 years after the volume reduction hepatectomy were 2.37 years, 71.8%, 34.0% and 17.0% in All, 4.71 years, 100%, 75% and 37.5% in Group.1 and 1.24 years, 60.7%, 16.2% and 8.1%

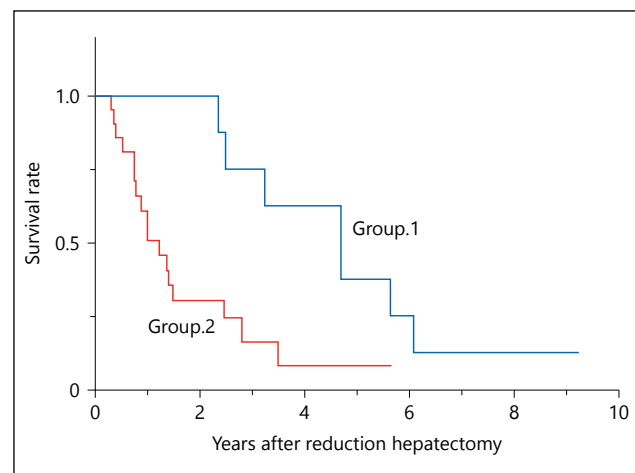


Fig. 1. (for Abstract no O-022).

in Group 2. **Conclusions:** Volume reduction hepatectomy improved the survival of patients with highly advanced HCC when the complete remission of the tumor was achieved by multidisciplinary treatment after the hepatectomy. Hepatectomy concomitant with multidisciplinary treatment should be considered even for highly advanced HCC.

O-023

Impact of Preoperative Body Composition on Outcomes After Hepatectomy for Hepatocellular Carcinoma

Toshimi Kaido¹, Yuhei Hamaguchi¹, Atsushi Kobayashi¹, Hisaya Shirai¹, Siyuan Yao¹, Shintaro Yagi¹, Naoko Kamo¹, Kojiro Taura¹, Shinji Uemoto¹

¹Kyoto University, Japan

Objective: To investigate the impact of preoperative body compositions including sarcopenia and visceral adiposity on outcomes after hepatectomy for hepatocellular carcinoma (HCC). **Methods:** We retrospectively analyzed 606 patients who underwent primary hepatectomy for HCC between April 2005 and March 2016. Skeletal muscle mass, muscle quality, and visceral adiposity were evaluated by skeletal muscle mass index (SMI), intramuscular adipose tissue content (IMAC), and the visceral to subcutaneous adipose tissue area ratio (VSR), respectively, using preoperative plain computed tomography imaging at the third lumbar vertebra level. The impact of these parameters on outcomes after hepatectomy for HCC was examined. **Results:** The overall survival rates were significantly lower in patients with low SMI ($P = 0.012$), high IMAC ($P < 0.001$), and high VSR ($P < 0.001$) than in patients with normal SMI, normal IMAC, and normal VSR, respectively. Similarly, the recurrence-free survival rate was significantly lower in patients with low SMI ($P = 0.009$), high IMAC ($P = 0.047$), and high VSR ($P = 0.016$) than in patients with normal SMI, normal IMAC, and normal VSR, respectively. Multivariate analysis showed that low SMI, high IMAC, and high VSR were independent risk factors for mortality and recurrence after hepatectomy for HCC. Moreover, preoperative sarcopenia obesity (defined as low SMI and visceral adipose tissue area $>100 \text{ cm}^2$) was an independent risk factor for death and HCC recurrence after hepatectomy. **Conclusion:** Preoperative abnormal body compositions had negative impact on outcomes after hepatectomy for HCC.

O-024

CCR9 as a Prognostic Marker and Therapeutic Target in Hepatocellular Carcinoma

Zhenhai Zhang¹

¹Shangdong University, China

The chemokine receptor CCR9 was recently implicated in tumor biology. In the present study, our objective was to evaluate the clinical significance and potential role of CCR9 in hepatocellular carcinoma HCC. CCR9 expression was detected by immunohistochemistry, quantitative PCR qPCR and western blotting in HCC patients. The prognostic significance of CCR9 expression was assessed. The functional roles of CCR9 in HCC were investigated using MTT, BrdU, colony formation assay and flow cytometry. CCR9 was significantly elevated in HCC tissue samples. High CCR9 expression was correlated with multiple tumor nodes, high Edmondson-Steiner grade and vascular invasion. Multivariate analysis showed that CCR9 expression was an independent prognostic factor for the overall survival (OS) of HCC patients.

O-025

A Case of Simultaneous Pancreatoduodenectomy and Living Liver Transplantation for Biliary Cancer Complicated with Congenital Biliary Dilatation

Masaaki Watanabe¹, Yasuyuki Koshizuka², Norio Kawamura², Ryoichi Goto², Hirofumi Kamachi², Toshiya Kamiyama², Tsuyoshi Shimamura³, Akinobu Taketomi²

¹Department of Transplant Surgery, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Japan, ²Department of general surgery I, Hokkaido university graduate school of medicine, Japan, ³Division of transplantation, Hokkaido University hospital, Japan

The patient, a 23-year-old woman, consulted a clinic with complaints of anorexia and epigastric discomfort. Close examinations indicated multiple biliary tract cancer complicated with congenital biliary dilatation (CBD) of Todani classification IVa. On CT scan, three papillary tumors were observed into the right hepatic duct, and they showed increased accumulation on FDG-PET. In contrast-enhanced US, another lesion with suspected cancer was also detected in the left hepatic duct. Although no clear lesions were found in the common bile duct, adenocarcinoma cells were detected by bile cytology and choledochal brush cytology. Preoperative diagnosis; Bp, tumor number 3 (22 mm, 20 mm, 19 mm), papillary dilatation, T1aN0M0, Stage I. Tumor resection by right lobe hepatectomy could not exclude the risk of postoperative liver failure, tumor recurrence due to bile leakage, and

carcinogenesis from the remaining left hepatic duct and common bile duct. Simultaneous pancreatoduodenectomy (PD) and living donor liver transplantation (LT) was selected to achieve complete removal of cancerous lesions without leaking bile. After the confirmation that peritoneal lavage cytology and lymph node metastasis (# 12, # 8) were pathologically negative, PD was performed without disconnecting the biliary tract, and tumors were extracted en-bloc with the whole liver. Husband's left lobe graft (Graft volume; 468 ml, GV/SV ratio; 42.6%) was transplanted thereafter. Operation time was 16 hours 22 minutes, blood loss was 1390 ml. Pathological finding; Bphd, papillary-infiltrating type, adenocarcinoma (pap>tub2>muc), pT2b, int, INFb, ly1α, v0 ne0, pN1 (#13a, 1/11), pEM0, pPV0, pA0, M0, Stage IIIB. The patient was discharged 3 weeks after operation with good functioning liver graft. She has been well without tumor recurrence during 28 months after operation under the treatment with S-1. This is the first report in Japan on simultaneous PD and LT for biliary tract cancer complicated with CBD.

O-026**Outcomes of Non-B Non-C Hepatocellular Carcinoma with Reference to Patients with Interferon-Induced Hepatitis C Virus Eradication**

Hiroji Shinkawa¹, Shogo Tanaka¹, Shigekazu Takemura¹, Ryosuke Amano¹, Kenjiro Kimura¹, Sadaaki Yamazoe¹, Go Ohira¹, Takayoshi Nishioka¹, Jun Tauchi¹, Tokuji Ito¹, Toru Miyazaki¹, Atsushi Ishihara¹, Shoji Kubo¹

¹Osaka City University, Japan

Purpose: This study aimed to evaluate survival outcomes in patients with non-B non-C hepatocellular carcinoma (NBNC-HCC) with reference to patients with HCC achieving sustained virological response (SVR) by preoperative interferon (IFN) treatment for chronic hepatitis C. **Methods:** We examined 781 patients who underwent hepatic resection for HCC. They were classified into NBNC-HCC, SVR-HCC, and non-SVR HCC groups. **Results:** Multivariate analysis for recurrence-free survival (RFS) and overall survival (OS) revealed that the adjusted hazard ratios (HR) of NBNC-HCC and non-SVR HCC groups with reference to the SVR-HCC group were 1.46 ($p = 0.10$) and 2.10 ($p < 0.001$), respectively, for RFS, and 1.69 ($p = 0.024$) and 2.11 ($p < 0.001$), respectively, for OS. Worsening of Child-Pugh grade at recurrence was confirmed in 21 patients (17.1%) with NBNC-HCC but not in those with SVR-HCC ($p = 0.017$, SVR vs. NBNC). In the NBNC-HCC group, hepatic resection for intrahepatic recurrence was adopted in 17.4% of patients without worsening of Child-Pugh grade at recurrence, whereas no hepatic resection was adopted in those with grade worsening. Among alcoholic hepatitis patients, Child-Pugh grade worsening at recurrence was more frequently observed in patients with sobriety than

those without sobriety (14.3% vs. 46.2%, $p = 0.049$). **Conclusions:** Compared to patients with SVR-HCC, those with NBNC-HCC had an increased risk for overall death. Worsening of background liver function may reduce the chance of re-hepatic resection and increase the risk for overall death in NBNC-HCC patients. For alcoholic hepatitis patients, sobriety may prevent deterioration of liver function after surgery.

O-027**Feasibility of Laparoscopic Liver Resection for Liver Cavernous Hemangioma: A Single-Institutional Comparative Study**

Youngheun Shin¹, Jaewon Joh¹,
Choonhyuck David Kwon¹, Gyuseong Choi¹,
Jongman Kim¹

¹Samsung Medical Center, Seoul, Korea

Background/Aim: While minimal invasive surgery has become popular, the feasibility of laparoscopy for liver cavernous hemangioma has not been shown. Studies that compared the feasibility of laparoscopic liver resection showed that, in general, laparoscopy may be superior to open surgery in blood loss and postoperative recovery despite the longer operation time. Although laparoscopic liver resection is one of the most interesting topics in the field of hepatic surgery, the feasibility of laparoscopic liver resection has focused on liver malignancies. Therefore, we designed this study to analyze the feasibility of laparoscopy for LCH (Liver Cavernous Hemangioma). **Method:** Patients who underwent hepatectomy for liver cavernous hemangioma from January 2008 to February 2019 at the Samsung Medical Center were reviewed. Patients who underwent trisectionectomy were excluded. Background characteristics, along with operative and postoperative recovery, were compared between the laparoscopy and open surgery groups. **Results:** Forty-one patients in the laparoscopy group and 35 patients in the open surgery group were compared. The differences in the background characteristics were age ($p = 0.027$), presence of symptoms (14.6% in laparoscopy vs. 57.1% in open, $P < 0.001$), albumin ($p = 0.006$), AST ($p = 0.013$) and tumor location (Rt, Lt and both side $p = 0.007$). The laparoscopy group had shorter operation time ($p = 0.036$), smaller blood loss ($p < 0.001$), lesser blood transfusion requirements ($p = 0.010$), lower level of post-operative total bilirubin, prothrombin time (INR) ($p = 0.002$, 0.001 each), shorter hospital stay ($p = 0.001$), earlier soft diet start ($p < 0.001$), earlier drain removal ($p < 0.001$) and shorter amount and duration of additional pain control ($p < 0.001$, $p = 0.010$ each). **Conclusion:** Laparoscopic liver resection for liver cavernous hemangioma can be safely performed with improved postoperative recovery except in tumors requiring trisectionectomy.

Table 1. Comparison on of the background characteristic between the laparos copy group and open surgery group. excluding patients who underwent trisectionectomy (for Abstract no O-027)

Variables	Laparoscopy (n = 41)	Open (n = 35)	Pvalue
Sex (M/F)	7/34	12/23	0.084
Age, median (years Q1-Q3)	44.0 (38.5–53.0)	54.0 (42.0–58.0)	0.027
Body mass index, median (kg/m ² Q1-Q3)	22.7 (20.3–24.3)	22.9 (21.5–25.3)	0.300
Indication for urgery (Symptom vs. other)			<0.001
Symptom	6 (14.6%)	20 (57.1%)	
Increase in size	32 (78.0%)	10 (28.6%)	
Possibility of malignancy	3 (7.3%)	5 (14.3%)	
ASA score			0.534
Class I	24 (58.5%)	18 (51.4%)	
Class II/III	17 (41.5%)	17 (48.6%)	
Major operation of upper abdomen (%)	3 (7.3%)	1 (2.9%)	0.620
Preoperative test			
Hemoglobin, median (g/dL)	12.6 (11.6–13.3)	12.8 (11.9–14.5)	0.488
Platelet, median (x10 ³ /μL)	215.0 (16.0–250.0)	199.0 (146.0–230.0)	0.167
Albumin, mean (g/dL)	4.52±0.27	4.29±0.41	0.006
Total bilirubin, median (mg/dL)	0.6 (0.3–0.8)	0.7 (0.5–1.3)	0.063
Aspartate aminotransferase, median (U/L)	18.0 (14.0–20.5)	21.0 (17.0–24.0)	0.013
Alanine aminotransferase, mediau (U/L)	13.0 (10.0–20.0)	16.0 (11.0–23.0)	0.207
Prothrombin time, INR, median (U/L)	1.00 (0.95–1.06)	1.02 (0.99–1.09)	0.124
Pathologic data			
Location			0.007
Right side	13 (31.7%)	22 (62.9%)	
Both	3 (7.3%)	2 (5.7%)	
Left side	25 (61.0%)	11 (31.4%)	
Number of tumors			
Single (%)	32 (78.0%)	28 (80.0%)	1.000
Multiple (%)	9 (22.0%)	7 (20.0%)	
Size median (cm Q1-Q3)	10.5 (6.1–14.0)	9.5 (7.0–15.0)	0.92
Surgical extent			0.082
Less than 4 Segments	21 (51.2%)	11 (31.4%)	
4 segment or more	20 (48.8%)	24 (68.6%)	

ASA, American Society of Anesthesiologists; INR, international normalized ratio.

O-028

The Role of Anatomical Hepatectomy in the Treatment of Intrahepatic Cholangiocarcinoma

Yingbin Liu¹, Xu'an Wang¹, Xiangsong Wu¹,
Wenguang Wu¹, Wei Gong¹

¹Xinhua hospital Shanghai Jiaotong University School of Medicine, China

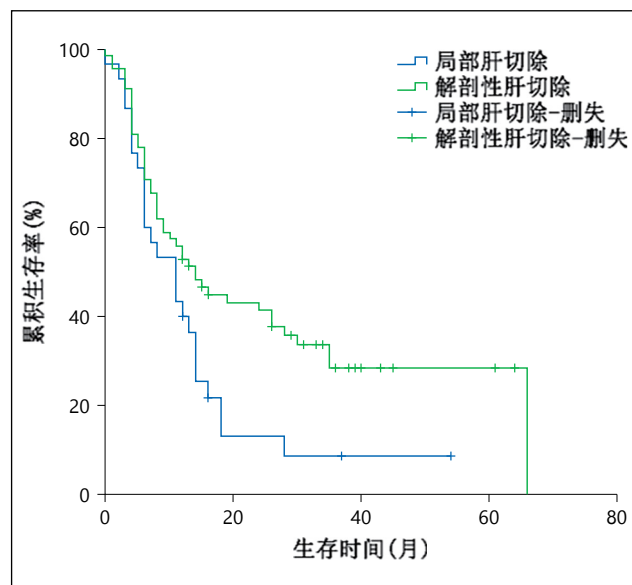
Objective To evaluate the role of anatomical hepatectomy in the treatment of intrahepatic cholangiocarcinoma. **Methods** The cases of intrahepatic cholangiocarcinoma who received curative surgery from 2010 to 2015 were analyzed retrospectively. Among the 98 patients enrolled in this study, 55 were male and 43 were female. The median age was 61 years. According to receiving anatomical hepatectomy or not, the 98 cases were divided

into two groups: non anatomical hepatectomy (n = 30) and anatomical hepatectomy (n = 68). The surgical results were compared between the two groups. Survival curves were plotted by the Kaplan Meier method and compared by the log rank test. The influence of each prognostic factor identified by univariate analysis was multivariate analysis by Cox's proportional hazard regression. Results The duration of surgery was significantly prolonged in the anatomical hepatectomy group (196.4±94.9) minutes vs. (166.2±65.7) minutes, P = 0.027. While there was no significant difference in terms of other surgical results such as intraoperative blood transfusion, postoperative morbidity and mortality rate. Compared to non anatomical hepatectomy, anatomical hepatectomy significantly improved long term survival results (14 months vs 11 months) (X²=4.641, P = 0.031). Single variable analysis indicated that tumor differentiation, tumor numbers, T stage, N stage, anatomical hepatectomy and adjuvant therapy significantly affected overall survival.

Table 2. Comparison of operative and postoperative recovery between the laparoscopy group and open surgery group, excluding patients who underwent trisectionectomy (for Abstract no O-027)

Variables	Laparoscopy (n = 11)	Open (n = 35)	P-value
Operative data			
Operation time, median (min)	213.6±106.0	265.1±103.8	0.036
Estimated blood loss, median (cc)	300.0 (100.0–400.0)	400.0 (250.0–1000.0)	<0.001
Transfusion (%)	1 (24%)	8 (22.9%)	0.010
Total bilirubin, median (mg/dL)	1.30 (0.85,1.70)	1.90 (1.40,2.30)	0.002
Aspartate aminotransferase, median (U/L)	160.0 (105.0,250.0)	209.0 (122.0,318.0)	0.371
Alanine aminotransferase, median (U/L)	163.0 (98.0,270.5)	166.0 (118.0,276.0)	0.574
Prothrombin time, INR median (U1)	1.23 (1.15,1.34)	1.36 (1.25,1.55)	0.001
Postoperative data			
Hospital stay, median (days)	7.0 (5.5,9.0)	9.0 (7.5,10.0)	0.001
Starting day of soft diet (days)	2.0 (1.0,2.0)	4.0 (3.0,4.0)	<0.001
Removal of drainage catheter (days)	4.0 (3.0,5.0)	5.0 (4.5,6.5)	<0.001
Amount of additional opioid (times)	1.0 (0.0,3.0)	3.0 (2.0,6.5)	<0.001
Last day for additional opioid (days)	2.0 (0.0,4.0)	3.0 (2.0,5.0)	0.010
Complications (%)	3 (7.3%)	5 (14.3%)	0.459
Clavien-Dindo classification			
None	38 (92.7%)	30 (85.7%)	0.326
I/II	2 (4.9%)	3 (8.6%)	
III/IV/V	1 (2.4%)	2 (5.7%)	

INR, international normalized ratio.

**Fig. 1.** (for Abstract no O-028).

Multivariate analysis demonstrated that tumor numbers (HR = 0.522, 95% CI: 0.259–0.974, $P = 0.042$) and anatomical hepatectomy (HR = 1.858, 95% CI: 1.092–3.161, $P = 0.022$) were two independent prognostic factors for overall survival. Conclusion Compared to non anatomical hepa-

tectomy, anatomical hepatectomy performed for intrahepatic cholangiocarcinoma is not only safe but also beneficial for long term survival.

O-029**Evaluation of the Significance of Anatomical Resection for Recurrent Hepatocellular Carcinoma**

Nobuhiro Harada¹, Takayuki Shiraki¹, Taku Aoki¹, Takashi Suzuki¹, Takao Arakawa¹, Kazuma Tago¹, Takayuki Shimizu¹, Kyung Hwa Park¹, Yuhki Sakuraoaka¹, Shozo Mori¹, Yukihiro Iso¹, Keiichi Kubota¹

¹Dokkyo Medical University, Japan

Background: The superiority of anatomical hepatic resection (AR) over non-anatomical partial hepatic resection (NAR) has been documented in terms of first hepatectomy for hepatocellular carcinoma (HCC). However, there have been few reports showing the superiority of AR in terms of second hepatectomy for recurrent HCC. The purpose of this study was to examine the significance of AR in second hepatectomies for HCC. **Methods:** Between April 2000 and August 2018, 986 patients with HCC underwent hepatic resections at our department. Of these, 167 resections were performed as second hepatectomy, and 100 patients with single recurrent

tumor were the subjects of the present study. The overall survival (OS) and recurrence-free survival (RFS) were examined among these patients in terms of the type of the resection (AR or NAR). **Results:** The AR group consisted of 28 patients, and 72 patients received NAR. In the AR group, subsegmentectomy was performed in 22 patients, segmentectomy in 4 patients and lobectomy in 2 patients. Among the background factors, there were significant differences in ICGR15 value ($P = 0.010$) and serum albumin level ($P = 0.046$) between the AR and NAR groups. There was no significant difference in OS ($P = 0.119$) or in RFS ($P = 0.212$) between the two groups. Therefore, we performed a propensity score matching adjusting the ICGR15 value and serum albumin level, and 56 patients (28 in the AR group and 28 in the NAR group) were selected. As a result, there was a tendency toward better OS in the AR group ($P = 0.075$), although RFS was similar between the two groups ($P = 0.854$). **Conclusions:** The results of the propensity score matching suggested the tendency that AR was associated with better OS. Although there was no significant difference, AR is recommended as the second hepatectomy procedure for recurrent HCC, when liver functional reserve allows an AR.

O-030

Laparoscopic Anatomical Liver Resections for Hepatocellular Carcinoma Using Glissonian Approach from the Liver Hilum; A Retrospective Analysis of 52 Patients

Kohei Mishima¹, Kazuharu Igarashi¹,
Giammauro Berardi¹, Kosuke Nakajima¹,
Takahiro Ozaki¹, Masayuki Honda¹, Go Wakabayashi¹

¹Ageo Central General Hospital, Japan

Background/Aim: Anatomical resections (AR) have been shown to improve the oncological outcomes by reducing local recurrence rate compared to non-anatomical resections in patients with HCC. However, few experiences on laparoscopic AR have been reported. In this study, we report the short-term outcomes after laparoscopic anatomical liver resections for hepatocellular carcinoma (HCC). **Methods:** We performed a retrospective analysis of 52 patients undergoing totally laparoscopic anatomical parenchymal sparing resections for HCC using glissonian approach from the hepatic hilum. **Results:** 42 patients had 1 lesion while HCC while 10 had two or more. A median size of tumors was 32 mm. Etiologies of HCC were hepatitis C virus infection (19 patients), hepatitis B virus infection (6 patients), alcohol (4 patients), and others (29 patients). All patients were in Child-Pugh A liver cirrhosis and median preoperative ICG (15)-% was 11. 34 subsectionectomies, 7 single sectionectomies, and 11 bisectionectomies were performed. Median operative time was 333 min and blood loss was 120 ml. 1 patient was converted to open surgery (1.9%). Blood transfusion was performed in 3 patients (5.8%). Median volume of resected

liver was 180 g. Postoperative complications (>C-D criteria IIIa) were seen in 4 patients (7.7%), with 90 days mortality in 1 patients (1.9%). Median postoperative stay was 11 days.

Conclusions: A precise preoperative planning and a standardized surgical technique allow surgeons to safely perform laparoscopic AR for HCC improving the oncological qualities and reducing surgical stress to patients. We will evaluate the long-term outcomes of HCC patients undergoing this procedure in the future.

Treatment: Clinical Trials

O-031

Safety and Efficacy of Lenvatinib by Starting Dose Based on Bodyweight in Patients With Unresectable Hepatocellular Carcinoma (uHCC) in REFLECT

Takuji Okusaka¹, Kenji Ikeda², Masatoshi Kudo³,
Richard S. Finn⁴, Shukui Qin⁵, Kwang-Hyub Han⁶,
Ann-Lii Cheng⁷, Fabio Piscaglia⁸, Masahiro Kobayashi²,
Max Sung⁹, Minshan Chen¹⁰, Lucjan Wyrwicz¹¹,
Jung-Hwan Yoon¹², Zhenggang Ren¹³, Corina Dutcus¹⁴,
Toshiyuki Tamai¹⁵, Min Ren¹⁴, Seiichi Hayato¹⁵,
Hiromitsu Kumada²

¹National Cancer Center Hospital, Japan, ²Toranomon Hospital, Japan, ³Kindai University Faculty of Medicine, Japan, ⁴Geffen School of Medicine, USA, ⁵Nanjing Bayi Hospital, China, ⁶Severance Hospital, Yonsei University, Korea, ⁷National Taiwan University Hospital, Taiwan, ⁸University of Bologna, Italy, ⁹Tisch Cancer Institute at Mount Sinai, USA, ¹⁰Sun Yat-sen University Cancer Center, China, ¹¹Centrum Onkologii-Instytut im. M. Skłodowskiej Curie, Poland, ¹²Seoul National University Hospital, Korea, ¹³Zhongshan Hospital Fudan University, China, ¹⁴Eisai Inc., USA, ¹⁵Eisai Ltd., Japan

Background: Lenvatinib (LEN) demonstrated statistical confirmation of noninferiority vs sorafenib (SOR) for overall survival (OS), and improved progression-free survival (PFS), time-to-progression, and objective response rate (ORR) in patients with uHCC in REFLECT. We report the efficacy and safety of LEN by weight-based starting dose. **Methods:** In REFLECT, patients with uHCC were randomized 1:1 to LEN (bodyweight <60 kg: 8 mg/d; bodyweight ≥60 kg: 12 mg/d; once daily) or SOR (400 mg twice daily). Efficacy (intention-to-treat) and safety (patients who received treatment) were analyzed by dose group. **Results:** Of 478 patients randomized to LEN, 151 (male, 70%; median age, 65 years) and 327 (male, 91%; median age, 62 years) were included in the starting-dose groups of 8 mg/d or 12 mg/d, respectively.

Table 1. (for Abstract no O-031)

Adverse event Percent (episodes/patient year)	<60 kg (8 mg)	60 kg (12 mg)
Hypertension	43 (0.79)	42 (0.78)
Diarrhea	35 (1.06)	40 (0.99)
Decreased appetite	33 (0.63)	35 (0.59)
Weight loss	29 (0.50)	32 (0.51)
Fatigue	28 (0.52)	31 (0.47)

Pharmacokinetic profiles were similar between groups. In the 8-mg group, 14% of patients were from Western regions; 86% from Asia-Pacific. In the 12-mg group, 42% were from Western regions; 58% from Asia-Pacific. Median OS was 13.4 (95% CI: 10.5–15.7) and 13.7 months (95% CI: 12.0–15.6); ORR was 22.2% and 24.9% for patients with bodyweight <60 kg and ≥60 kg, respectively. Median PFS was 7.4 months in both groups. Median duration of treatment: 8-mg group, 5.6 months; 12-mg group, 6.3 months. Mean LEN relative dose intensity: 8-mg group, 87.7%; 12-mg group, 87.5%. Common any-grade adverse events by bodyweight (dose) are shown in the Table. **Conclusions:** LEN efficacy was comparable between groups. Exposure to LEN was greater for the 12-mg vs 8-mg group. When AEs were adjusted by treatment duration, no notable differences were observed in the AE profiles between the 2 starting doses. Altogether, these results support the 8-mg and 12-mg starting doses based on bodyweights of <60 kg and ≥60 kg, respectively, in REFLECT.

O-032**Analysis of Survival and Objective Response (OR) in Patients With Hepatocellular Carcinoma in a Phase 3 Study of Lenvatinib (REFLECT)**

Matasatoshi Kudo¹, Richard S. Finn², Shukui Qin³, Kwang-Hyub Han⁴, Kenji Ikeda⁵, Ann-Lii Cheng⁶, Fabio Piscaglia⁷, Kazuomi Ueshima¹, Hiroshi Aikata⁸, Arndt Vogel⁹, Carlos Lopez¹⁰, Marc Pracht¹¹, Zhiqiang Meng¹², Bruno Daniele¹³, Joong-Won Park¹⁴, Daniel Palmer¹⁵, Corina Dutcus¹⁶, Toshiyuki Tamai¹⁷, Kenichi Saito¹⁶, Riccardo Lencioni^{18,19}

¹Kindai University Faculty of Medicine, Japan, ²Geffen School of Medicine, UCLA Medical Center, USA, ³Nanjing Bayi Hospital, China, ⁴Severance Hospital, Yonsei University, Korea, ⁵Toranomon Hospital, Japan, ⁶National Taiwan University Hospital and National Taiwan University Cancer Center, Taiwan, ⁷University of Bologna, Italy, ⁸Hiroshima University Hospital, Japan, ⁹Hannover Medical School, Germany, ¹⁰Marques de Valdecilla University Hospital, Spain, ¹¹Cancer Institute Eugene Marquis, France, ¹²Fudan University, Shanghai Cancer Center, China, ¹³Ospedale del Mare, Italy, ¹⁴National Cancer Center Korea, Korea, ¹⁵The Clatterbridge Cancer Centre, UK, ¹⁶Eisai Inc., USA, ¹⁷Eisai Co., Ltd., Japan, ¹⁸University of Pisa School of Medicine, Italy, ¹⁹Miami Cancer Institute, USA

Background: In REFLECT, lenvatinib (LEN) demonstrated treatment effect on overall survival (OS) by statistical confirmation of noninferiority to sorafenib (SOR). OR rates for LEN vs SOR were: 24% vs 9% by investigator review and 41% vs 12% by independent review (Kudo M et al, *Lancet*, 2018). As the relationship between OR and OS in phase 3 hepatocellular carcinoma (HCC) studies is unclear, we explored the relationship between OR and OS in REFLECT. **Methods:** OR assessed by investigators per modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used to analyze the association between OR and OS of patients treated with LEN or SOR. The median OS of responders (with complete response or partial response) was compared to that of nonresponders (with stable disease, progressive disease, or unknown/not evaluable) irrespective of treatment. Landmark analyses were performed by OR status at several fixed time points as sensitivity analyses, and the effect on OS was evaluated by Cox regression with OR as a time-dependent covariate with other prognostic factors. **Results:** Median OS was 22.4 months for responders and 11.4 months for nonresponders. Hazard ratios (HR) of landmark analyses at 2, 4, and 6 months were 0.75 (95% confidence interval [CI], 0.57–0.98), 0.72 (95% CI, 0.56–0.92), and 0.73 (95% CI, 0.57–0.93), respectively. Independent predictors of OS based on unstratified Cox regression are summarized in the Table. **Conclusions:** In REFLECT, OR was an independent predictor of OS in patients with HCC regardless of treatment. The results indicate that this correlation is worth further investigation.

Table 1. (for Abstract no O-032)

Parameter	Univariate analysis		Multivariate analysis	
	HR [95% CI]	P-value	HR [95% CI]	P-value
Macroscopic portal vein invasion (yes vs no)	1.55 [1.30–1.85]	<0.001	1.37 [1.14–1.64]	<0.001
Baseline AFP (ng/ml) (<200 vs ≥200)	0.52 [0.45–0.61]	<0.001	0.56 [0.48–0.66]	<0.001
No. of tumor sites at baseline (2 vs 1)	1.46 [1.23–1.73]	<0.001	1.40 [1.18–1.66]	<0.001
No. of tumor sites at baseline (≥3 vs 1)	2.24 [1.84–2.72]	<0.001	2.02 [1.66–2.47]	<0.001
Involved tumor site-liver (yes vs no)	2.31 [1.67–3.20]	<0.001	1.68 [1.20–2.33]	0.002
Etiology HBV (yes vs no)	1.23 [1.06–1.43]	0.006	1.20 [1.03–1.39]	0.019
Prior procedure for HCC (yes vs no)	0.67 [0.57–0.77]	<0.001	0.84 [0.72–0.99]	0.032
Treatment (LEN vs SOR)	0.93 [0.80–1.077]	0.326	0.85 [0.73–0.996]	0.044
OR (yes vs no)	0.61 [0.49–0.76]	<0.001	0.61 [0.49–0.76]	<0.001

O-033
Nivolumab in Patients with Advanced Hepatocellular Carcinoma (aHCC) and Child-Pugh (CP) B Status: Japanese Subanalysis from the CheckMate 040 Study

Masatoshi Kudo¹, Ana Matilla², Armando Santoro³, Ignacio Melero⁴, Antonio Cubillo Gracian⁵, Mirelis Acosta-Rivera⁶, Su-Pin Choo⁷, Anthony B. El-Khoueiry⁸, Ryoko Kuromatsu⁹, Bassel El-Rayes¹⁰, Kazushi Numata¹¹, Yoshito Itoh¹², Francesco Di Costanzo¹³, Oxana Cryslar¹⁴, Maria Reig¹⁵, Hideaki Takahashi¹⁶, Yun Shen¹⁷, Jaclyn Neely¹⁷, Jeffrey Anderson¹⁷, Bruno Sangro¹⁸

¹Kindai University Faculty of Medicine, Osaka, Japan, Japan, ²Servicio de Digestivo, Hospital General Universitario Gregorio Marañon, Madrid, Spain, Spain, ³Istituto Clinico Humanitas, Rozzano, Italy, Italy, ⁴Universidad de Navarra, Pamplona, Spain, Spain, ⁵Hospital Universitario HM Sanchinarro, Centro Integral Oncologico Clara Campal CIOCC, Madrid, Spain, Spain, ⁶Fundacion de Investigacion, San Juan, Puerto Rico, Puerto Rico, ⁷National Cancer Center, Singapore, Singapore, ⁸USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA, USA, ⁹Kurume University Hospital, Fukuoka, Japan, Japan, ¹⁰Emory University Winship Cancer Institute, Atlanta, GA, USA, USA, ¹¹Yokohama City University Medical Center, Yokohama, Japan, Japan, ¹²Kyoto Prefectural University of Medicine, Kyoto, Japan, Japan, ¹³AOU Careggi, Florence, Italy, Italy, ¹⁴University of Michigan, Ann Arbor, MI, USA, USA, ¹⁵BCLC Group, Liver Unit, Hospital Clinic de Barcelona, CIBEREHD, Barcelona, Spain, Spain, ¹⁶National Cancer Center Hospital East, Kashiwa, Japan, Japan, ¹⁷Bristol-Myers Squibb, Princeton, NJ, USA, USA, ¹⁸Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain, Spain

Background/Aim: Patients with CP-B aHCC are often excluded from clinical trials due to their poor prognosis. Median overall survival (OS) for these patients when treated

with sorafenib is approximately 3–5 months in retrospective/descriptive studies; thus, novel treatment options are needed. Nivolumab, a PD-1 inhibitor, is approved in several countries for sorafenib-treated patients with aHCC based on CheckMate 040 (NCT01658878; El-Khoueiry Lancet 2017). We report data from the CP-B cohort of CheckMate 040, the first prospective study of immunotherapy in these patients. **Methods:** Sorafenib-naïve (n = 25) or -treated (n = 24) patients with CP-B7-B8 aHCC received nivolumab 240 mg IV for 30 min Q2W until unacceptable toxicity/disease progression. Of the total patients, 17 were Japanese. Primary endpoints were objective response rate (ORR) (investigator-assessed, RECIST v1.1) and duration of response (DOR). Safety was assessed in all treated patients using NCI CTCAE v4.0. **Results:** Median (range) follow-up was 16.3 (11.0–22.5) months. Overall, 28/49 (57.1%) patients had vascular invasion/extrahepatic spread. Investigator-assessed ORR was 12.2% (6/49) and disease control rate (DCR) was 55.1%. Median (m) time to response was 2.7 months and mDOR was 9.9 months; 1 patient had ongoing response at data cutoff. The mOS was 7.6 months (9.8 and 7.4 months for sorafenib-naïve and -treated patients, respectively). Treatment-related adverse events (TRAEs) were reported in 25 (51%) patients; 4 (8.2%) patients had select hepatic TRAEs. TRAEs led to discontinuation in 2 (4.1%) patients. The safety profile was comparable to patients with CP-A aHCC. Data from the Japanese subpopulation will be presented. **Conclusions:** Patients with CP-B aHCC treated with nivolumab had encouraging DCR and durable responses. AEs were manageable and did not lead to higher discontinuation versus patients with CP-A aHCC. Nivolumab showed promising efficacy and tolerability compared with historical data, supporting further investigation.

O-034

Atezolizumab + Bevacizumab in Previously Untreated Patients with Unresectable or Advanced Hepatocellular Carcinoma: Analysis of a Phase Ib Study

Michael S. Lee¹, Baek-Yeol Ryoo², Chih-Hung Hsu³, Kazushi Numata⁴, Stacey Stein⁵, Wendy Verret⁶, Steve Hack⁶, Jessica Spahn⁶, Bo Liu⁶, Heba Abdullah⁶, Aiwu Ruth He⁷, Kyung-Hun Lee⁸

¹UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, ²Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, ³National Taiwan University Hospital, Taipei, Taiwan, ⁴Yokohama City University Medical Center, Yokohama, Japan, ⁵Yale School of Medicine, New Haven, CT, USA, ⁶Genentech, Inc., South San Francisco, CA, USA, ⁷Georgetown University Medical Center, Washington, DC, USA, ⁸Seoul National University Hospital, Seoul, Korea

Background: Unresectable or advanced hepatocellular carcinoma (HCC) is a lethal disease with limited treatment options; tyrosine kinase inhibitors targeting angiogenesis are the mainstay in the first-line setting. In addition to its anti-angiogenic activity, bevacizumab (anti-VEGF) has immunomodulatory effects that alter the tumour microenvironment. Through this activity, bevacizumab may augment anti-tumour immune responses mediated by atezolizumab (anti-PD-L1). This mechanism of action provides a strong scientific rationale to combine atezolizumab + bevacizumab in a cohort of patient with unresectable or advanced HCC (Arm A). **Methods:** Arm A of the Phase Ib study G030140 (NCT02715531) enrolled patients with unresectable or advanced HCC who were naive to systemic treatment. Patients in arm A received 1200 mg atezolizumab + 15 mg/kg bevacizumab intravenously q3w until unacceptable toxicity or loss of clinical benefit. Primary endpoints were safety and independent review facility [IRF]-assessed objective response rate (ORR) per RECIST 1.1. Secondary endpoints included progression-free survival (PFS) and duration of response (DOR) assessed by investigators (INV) per RECIST 1.1 and by IRF per RECIST 1.1 and HCC mRECIST; INV-assessed ORR per RECIST 1.1; IRF-assessed ORR per HCC mRECIST, as well as overall survival. **Anticipated Results:** Enrolment (n = 104) was completed in July 2018. Safety and efficacy data will be presented, with an estimated minimum follow-up of 10 months. Results are expected to be available in early August 2019.

O-035

Association Between Overall Survival and Adverse Events with Lenvatinib Treatment in Patients with Hepatocellular Carcinoma (REFLECT)

Max Sung¹, Richard S. Finn², Shukui Qin³, Kwang-Hyub Han⁴, Kenji Ikeda⁵, Ann-Lii Cheng⁶, Masatoshi Kudo⁷, Ryosuke Tateishi⁸, Masafumi Ikeda⁹, Valery Breder¹⁰, Kun-Ming Rau¹¹, Yuk Ting Ma¹², Angel Alsina¹³, Baek-Yeol Ryoo¹⁴, Zhenggang Ren¹⁵, Kalgi Mody¹⁶, Corina Dutcus¹⁶, Toshiyuki Tamai¹⁷, Kenichi Saito¹⁶, Fabio Piscaglia¹⁸

¹Tisch Cancer Institute at Mount Sinai, USA, ²Geffen School of Medicine, UCLA Medical Center, USA, ³Nanjing Bayi Hospital, China, ⁴Severance Hospital, Yonsei University, Korea, ⁵Toranomon Hospital, Japan, ⁶National Taiwan University Hospital and National Taiwan University Cancer Center, Taiwan, ⁷Kindai University Faculty of Medicine, Japan, ⁸The University of Tokyo Hospital, Japan, ⁹National Cancer Center Hospital East, Japan, ¹⁰National Medical Research Center of Oncology n, a, Russia, ¹¹E-DA Hospital, Taiwan, ¹²Queen Elizabeth Hospital, UK, ¹³Tampa General Hospital, USA, ¹⁴Asan Medical Center, University of Ulsan College of Medicine, Korea, ¹⁵Zhongshan Hospital Fudan University, China, ¹⁶Eisai Inc., USA, ¹⁷Eisai Co., Ltd, Japan, ¹⁸University of Bologna, Italy

Background: In the phase 3 REFLECT study, lenvatinib (LEN) demonstrated a treatment effect on overall survival (OS) by statistical confirmation of noninferiority to sorafenib (SOR) in patients with unresectable hepatocellular carcinoma (uHCC), who had not received prior treatment for advanced disease (Kudo M et al, *Lancet* 2018). LEN is approved in several major markets for the first-line systemic treatment of uHCC. The most common adverse events (AEs) in patients treated with LEN were hypertension and diarrhea. In addition, LEN showed a different AE profile from that of SOR. Patients who received LEN experienced more instances of hypertension, proteinuria, dysphonia, and hypothyroidism than patients who received SOR. Recently, hypertension in LEN-treated patients with differentiated thyroid cancer was shown to be correlated with improved efficacy. Here we report the post hoc analysis exploring whether AEs associated with LEN were correlated with longer OS in REFLECT. **Methods:** 478 Patients were randomized to receive LEN (12 mg/d for actual body weight ≥ 60 kg or 8 mg/d for actual body weight < 60 kg). Subgroup analyses were conducted based on whether patients treated with LEN experienced any-grade AEs of interest (AEIs). OS was estimated by the Kaplan-Meier method. **Results:** The AEIs in patients treated with LEN were hypertension (42%), diarrhea (38%), proteinuria (24%), dysphonia (24%), and hypothyroidism (16%). OS was longer in patients who had one of several AEIs than in those who did not (Table). **Conclusions:** In this post hoc exploratory analysis of patients

Table 1. Adverse Events of Interest (for Abstract no O-035)

Adverse event	AEI, n (%)	No AEI, n (%)	Hazard Ratio for OS	95% CI	P-value
Hypertension	201 (42%)	277 (58%)	0.64	0.52–0.80	0.00005
Diarrhea	184 (38%)	294 (62%)	0.72	0.58–0.90	0.00314
Proteinuria	117 (24%)	361 (76%)	0.76	0.60–0.98	0.03042
Dysphonia	113 (24%)	365 (76%)	0.86	0.68–1.11	0.24708
Hypothyroidism	78 (16%)	400 (84%)	0.72	0.54–0.96	0.02377

with uHCC treated with LEN, the occurrence of hypertension, diarrhea, proteinuria, or hypothyroidism was generally associated with longer OS. The potential for confounding factors at baseline should be further investigated.

Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy

O-036

Comparison between Stereotactic Body Radiotherapy and Radiofrequency Ablation as First Therapy for Small Hepatocellular Carcinoma

Baek Gyu Jun¹, Young Don Kim¹, Gab Jin Cheon¹, Jeong-Ju Yoo², Sang Gyune Kim², Young Seok Kim², Soung Won Jeong³, Jae Young Jang³, Hong Soo Kim⁴, Sae Hwan Lee⁴

¹University of Ulsan College of Medicine, Korea,

²Soonchunhyang University College of Medicine

Bucheon Hospital, Korea, ³Soonchunhyang University College of Medicine Seoul Hospital, Korea,

⁴Soonchunhyang University College of Medicine Cheonan Hospital, Korea

Background/Aim: Resection or ablative therapy is not indicated for many patients with hepatocellular carcinoma (HCC) because of advanced cirrhosis or tumor location. Stereotactic body radiotherapy (SBRT) may be an alternative treatment for these patients. This study compared the therapeutic effects of radiofrequency ablation (RFA) and SBRT in patients with small (3 cm) HCC. **Methods:** Data of HCC patients who underwent SBRT or RFA as an initial treatment at two tertiary referral hospitals between March 2011 and February 2017 were reviewed. The patient inclusion criteria were a single nodule measuring ≤ 3 cm in size and not suitable for

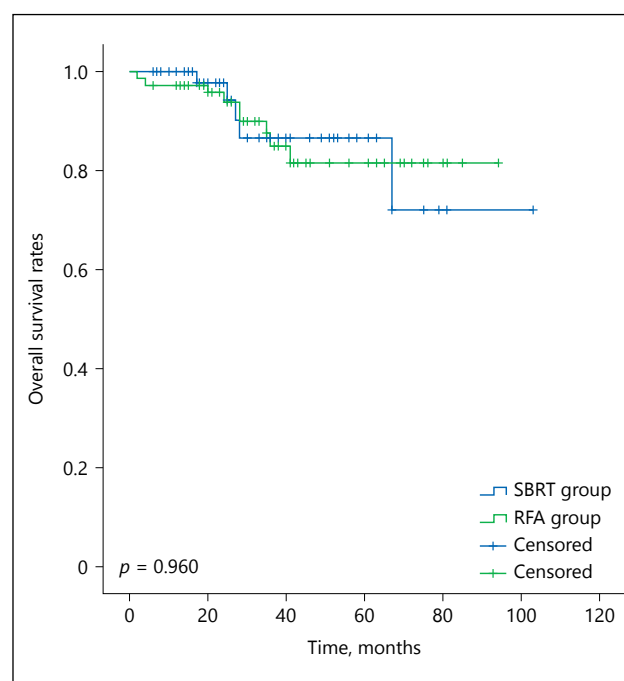


Fig. 1. Overall survival of all patients in the SBRT and RFA groups (for Abstract no O-036).

resection. **Results:** SBRT and RFA were performed in 57 (SBRT group) and 73 (RFA group) patients, respectively. In the SBRT group, 21 patients received SBRT only and 36 received SBRT combined with transarterial chemoembolization. The one-, three- and five-year overall survival rates were 97.7%, 86.4%, and 72.0%, respectively, in the SBRT group compared with 97.3%, 87.5% and 81.5%, respectively, in the RFA group, with no significant difference between the two groups ($P = 0.960$). The estimated one-, three- and five-year progression-free survival rates were 87.4%, 64.8% and 49.4%, respectively, in the SBRT group and 84.8%, 70.8% and 52.6%, respectively, in the RFA group ($P = 0.712$). Liver toxicity after treatment did not differ significantly between the SBRT (8.8%, 5/57) and RFA (2.7%, 2/71) groups ($P = 0.131$). **Conclusion:** SBRT is an effective and safe treatment method for small HCCs, with survival and tumor recurrence rates similar to those of RFA.

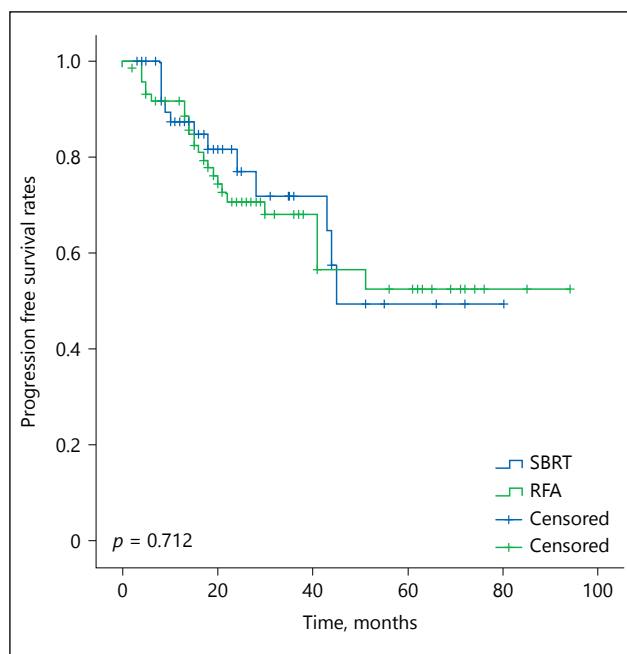


Fig. 2. Progression-free survival of all patients in the SBRT and RFA groups (for Abstract no O-036).

O-037

Impact of Scores of Child-Pugh Classification on Overall Survival After Stereotactic Body Radiation Therapy for Primary and Metastatic Liver Tumors

Osamu Tanaka¹, Takao Kojima¹, Akihiro Ohbora¹, Takuya Taniguchi¹, Kousei Ono¹, Chiyoko Makita², Masayuki Matsuo²

¹Asahi University Hospital, Japan, ²Gifu University Hospital, Japan

Introduction: Stereotactic body radiotherapy (SBRT) delivers high-dose radiation to tumor tissue in a few fractions, thereby reducing radiation damage to at-risk organs. There are more potential effects in SBRT because of the higher biological equivalent dose delivered, we retrospectively analyzed its effectiveness and toxicity at our institution. **Materials and Methods:** Data from patients with hepatocellular carcinoma (HCC; n = 10) and liver metastases (n = 10) who underwent SBRT (total dose of 30–50 Gy in 5–10 fractions) between 2013 to 2016 were analyzed. Adverse events were recorded at the end of RT, 6 months after treatment, or upon death. Overall survival (OS) was calculated according to the biological effective dose (BED) and liver function [Child-Pugh (CP) classification 5 or 6 v.s. 7 or 8] after SBRT using Kaplan-Meier analyses. **Results:** Six of 20 patients declined CP classification score after SBRT, and grade 3 adverse events did not occur in any patient. A higher OS rate was seen in patients receiving higher biological effective

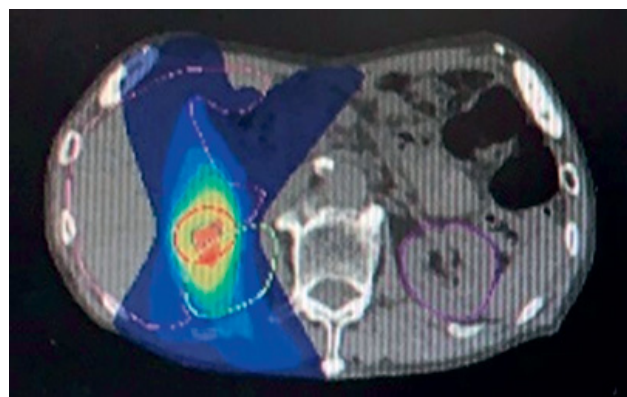


Fig. 1. Overall survival of all patients in the SBRT and RFA groups (for Abstract no O-037).

dose (BED) and in those with better CP classification after SBRT. Kaplan-Meier survival analysis yielded a median OS of 401 days and 1- and 2-year OS of 45% and 15%, respectively. **Conclusion:** Higher BED was significantly associated with tumor control and there were no differences in tumor control rate between HCC and metastatic tumors. Changes in CP scores after SBRT also affected survival rate, and good liver function may permit multiple rounds of SBRT.

O-038

A Systematic Review and Meta-Analysis of Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: The Correlation of Radiation Dose and Overall Survival Rate

Kyung Ran Park¹, Gyu Ri Kim², Ik Jae Lee³, Jung Mo Nam²

¹Department of Radiation Oncology, Kosin University College of Medicine, Korea, ²Department of Preventive Medicine, Yonsei University College of Medicine, Korea, ³Department of Radiation Oncology, Yonsei University College of Medicine, Korea

Background/Aim: Stereotactic body radiation therapy (SBRT) is currently becoming a therapeutic option in the management of hepatocellular carcinoma (HCC). The studies on HCC patients treated with SBRT have demonstrated local control rates of 70–100% with various doses and fractionation schemes of SBRT. The aim of this study was to investigate the association of SBRT dose with overall survival (OS) rate. **Methods:** A systematic search of medical literature databases was performed on patients receiving SBRT for HCC. A total of 28 studies presenting median dose and number of fractions of SBRT and 1, 2, or 3 year overall survival rate were reviewed. The effect size of overall survival rate was calculated by random effect model. Logistic regression analysis was used to examine the correlation between median equivalent dose in 2

Gy fractions (EQD2) of SBRT and overall survival rate. **Results:** The pooled 1, 2, and 3 year OS rates were 81% (95% confidence interval [CI]: 76–86), 62% (95% CI 55–70), and 48% (95% CI 39–57), respectively. The greater median EQD2 was positively associated with increases in OS rate; for each one-unit increase in median EQD2, the odds of OS rate increased by 1.5% (odds ratio 1.015; 95% CI 1.008 to 1.022; $P < 0.001$) for 1 year OS rate, 1.3% (odds ratio 1.013; 95% CI 1.007 to 1.019; $P < 0.001$) for 2 year OS rate, 1.4% (odds ratio 1.014; 95% CI 1.007 to 1.021; $P < 0.001$) for 3 year OS rate. **Conclusion:** This study showed that the greater median EQD2 of SBRT was significantly associated with higher 1, 2, and 3 year OS rates.

O-039

Prognostic Factors in Advanced Hepatocellular Carcinoma (HCC) of 10 cm Treated with Stereotactic Body Radiotherapy (SBRT)

C.L. Chiang^{1,2,3}, Natalie S.M. Wong¹, Cynthia S.Y. Yeung¹, Connie H.M. Ho¹, Winnie W.Y. Yip¹, Jennifer S.K. Ha², Mark K.H. Chan⁴, Venus W.Y. Lee¹, Frank C.S. Wong¹, Francis A.S. Lee¹

¹Tuen Mun Hospital, Hong Kong SAR, China, ²The University of Hong Kong, Hong Kong SAR, China, ³HKU-Shenzhen Hospital, Hong Kong SAR, China, ⁴Imperial College London NHS Healthcare Trust, UK

Purpose: The role of stereotactic body radiotherapy (SBRT) is evolving in patients with hepatocellular carcinoma (HCC). This study is to evaluate the efficacy of SBRT in advanced HCC population and identify the predictive factors of overall survival. **Patients and Methods:** This is a retrospective study that included all patients treated with SBRT from 2006 to 2017. Data were retrieved from a prospective collected database. All patients had advanced HCC >5 cm ineligible for curative interventions and Child-Pugh (CP) score A5 to B7. The SBRT dose range was 4Gy in 6 to 10 fractions. The primary endpoint is overall survival (OS). **Results:** A total of 156 patients were evaluable. Underlying liver disease was hepatitis B in 80.1% of patients. The median tumor size was 12.2 cm (range: 5.0–25.7 cm). Tumor vascular thrombosis was present in 48.1% and extra-hepatic disease was present in 31.4%; 17.3% had CP class B disease. The median total equivalent dose in 2Gy per fraction (EQD2, $a/b = 10$) was 32.7Gy (4Gy in 7 fractions). The median OS and 1-year overall survival rate and local control rate was 44.2%, (95% CI: 36.4%–52.0%) and 83.5 % (95% CI: 76.7%–90.4%) respectively. Under multivariate analysis, extra-hepatic metastases (hazard ratio HR: 2.1, range: 1.38–3.3, $p = 0.001$), AFP level (HR: 2.6, range 1.75–4.06, $p < 0.001$), number of lesions (HR: 2.4, range 1.34–40.29), and post-SBRT therapy (HR: 0.32, range: 0.17–0.6, $p < 0.001$) were independently predicting OS. Treatment responder of SBRT (CR+PR) was

independently associated with better local control (HR: 2.8, range: 1.0–5.5, $p = 0.04$) and a trend towards improved OS (HR: 1.4, range: 0.95–2.09, $p = 0.09$). **Conclusion:** In advanced HCC population with median size of tumor >10 cm, SBRT provides favorable survival outcome. Patients who responded to SBRT and received further systemic therapy had better survival. Further study to combine both is warranted.

O-040

Dynamic Contrast-Enhanced and Intravoxel Incoherent Motion MRI May Predict Overall Survival in Patients with Advanced Hepatocellular Carcinoma Receiving Lenalidomide as Second-Line Therapy

Bang-Bin Chen¹, Yu-Yun Shao², Zhong-Zhe Lin², Chih-Hung Hsu², Ann-Li Cheng², Chiun Hsu², Po-Chin Liang¹, Tiffany Ting-Fang Shih¹

¹Department of Medical Imaging, National Taiwan University Hospital, Taiwan, ²Departments of Oncology, National Taiwan University Hospital, Taiwan

Background: To prospectively predict survival outcome using image biomarkers from dynamic contrast-enhanced (DCE)-MRI and intravoxel incoherent motion (IVIM) diffusion-weighted image (DWI) in patients with advanced hepatocellular carcinoma (HCC) receiving lenalidomide as 2nd-line therapy. **Methods:** Forty-four patients with advanced HCC who had documented progression after sorafenib treatment were enrolled and received lenalidomide as 2nd-line therapy. Pre-treatment MR image biomarkers, obtained from DCE-MRI (Peak, Slope, AUC, Ktrans, Kep, Ve) and IVIM DWI [Apparent diffusion coefficient (ADC), diffusion coefficient (D), pseudo-diffusion coefficient (D^*), and perfusion fraction (f)], were obtained by placing regions of interest in the largest area of the tumor. The relationship between these biomarkers, as well as peripheral immune cells, was assessed by using the Pearson correlation test. By using the Cox proportional hazards model for univariate and multivariate analyses, the association of imaging biomarkers with progression-free survival (PFS) and overall survival (OS) was investigated. **Results:** The median PFS and OS was 2.3 and 8.0 months, respectively. Peripheral CD8+ cells were significantly positively correlated with ADC ($r = 0.411$, $P = 0.003$) and f ($r = 0.266$, $P = 0.041$). DCE-MRI biomarkers did not correlate with any peripheral immune cells. Among all MR imaging biomarkers, patients with high values of Slope ($P = 0.033$), ADC ($P = 0.041$) and f ($P = 0.011$) had longer OS than did those with low values. No association of image biomarker with PFS was found. Cox multivariate analysis revealed that Slope ($P = 0.034$) and f ($P = 0.011$) remained independent predictors of OS after adjusting for age, sex, tumor size, Eastern Cooperative Oncology Group and Child-Pugh score. **Conclusions:** Both pre-treatment DCE-MRI and IVIM DWI image biomarkers may

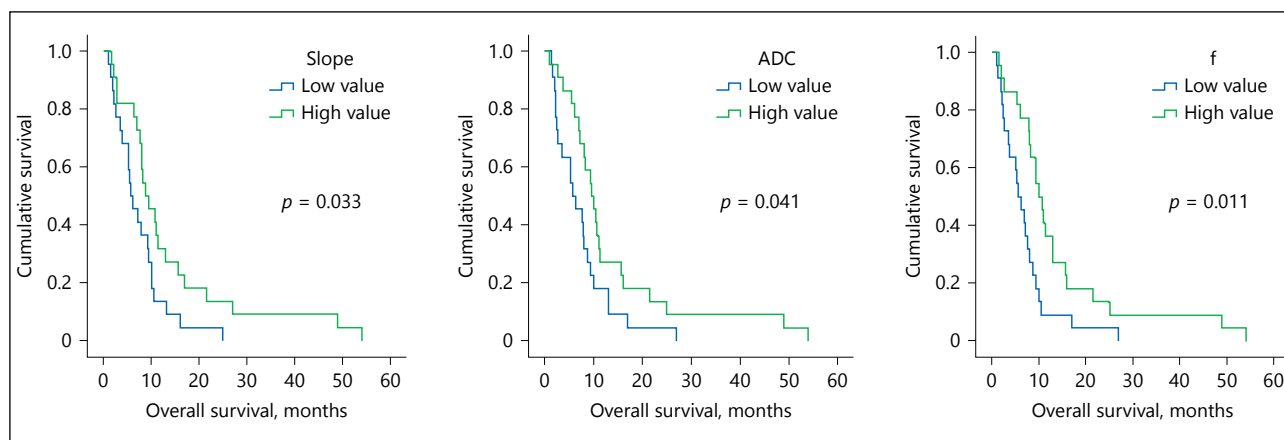


Fig. 1. (for Abstract no O-040).

predict OS in patients receiving lenalidomide as 2nd-line therapy. The IVIM DWI image biomarkers may be associated with its immunomodulatory effect.

Treatment: Systemic, Targeted, Novel Target or Experimental Therapy

O-041

Enhancement of Delivery System for Anti-Cancer Drugs in Hepatocellular Carcinoma (HCC) Using Phenylboronic Acid Conjugated Doxorubicin Nanocomplex

Seung Kew Yoon¹, Byung-Yoon Kang¹, Sung Min Kim¹, Wonhee Hur¹, Won Jong Kim²

¹The Catholic University Liver Research Center & WHO Collaborating Center of Viral Hepatitis, College of Medicine, The Catholic University of Korea, Seoul, Korea, ²Department of Chemistry, Pohang University of Science and Technology, Pohang 37673, Korea

Background/Aims: Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third-highest cause of cancer-related death. Various therapeutic approaches have been proposed in an attempt to prolong survival of advanced HCC patients using different anti-cancer drugs or delivery systems. We have previously reported that Phenylboronic acid (PBA) targets molecules highly expressed in tumor cells. In this study, we investigated the ways to maximize the efficiency of delivery of anti-cancer drugs in HCC. **Methods:** In vitro cytotoxicity of the nanocomplex with PBA conjugated

doxorubicin (Dox), Dox and PBA alone in various HCC cells was assayed by MTT assay. Using the xenograft and orthotopic model, the anti-cancer effect of nanocomplex was evaluated by measuring the tumor size and MR imaging. Serum AFP, ALT and creatinine levels were measured in those mice. **Results:** The cytotoxicity of the nanocomplex increased dependent on its concentration. At low concentrations, nanocomplex showed higher cytotoxicity than DOX alone in liver cancer cells. On the other hand, PBA itself have no cytotoxicity in liver cells. *In vitro*, nanocomplex showed higher targetability in liver cancer cells by fluorescent imaging. *In vivo* experiments using bioimaging showed that the nanocomplex was more efficiently delivered to the tumor. In the Xenograft and orthotopic model, the tumor size decreased than DOX alone group. In addition, AFP in nanocomplex group significantly decreased, but ALT and creatinine levels were within normal range. These results showed that nanocomplex exhibits better anti-cancer effects than DOX alone but does not cause liver and kidney toxicity. **Conclusions:** The improved therapeutic effect of the nanocomplexes can be explained by active targeting via the enhanced cellular uptake by residual PBA moieties, and drug release in the intracellular environment. Nanocomplex have potent and specific anti-cancer effects on liver cancer cells. The overall results suggest therapeutic potential of nanocomplexes in liver cancer therapy.

O-042

Safety of Tepotinib in Patients with MET Overexpressing (MET+) Advanced Hepatocellular Carcinoma (HCC): Outcomes from Two Studies

Shukui Qin¹, Baek-Yeol Ryo², *Thomas Decaens*³,
Rolf Bruns⁴, Dongli Zhou⁵, Juergen Scheele⁶,
Karin Berghoff⁷, Sandrine Faivre⁸

¹PLA Cancer Center, Nanjing Bayi Hospital, Nanjing, China; ²Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; ³Department of hepatogastroenterology, Université Grenoble-Alpes, CHU Grenoble-Alpes, Institute for Advanced Biosciences, Grenoble, France; ⁴Biostatistics Oncology, Merck Healthcare KGaA, Darmstadt, Germany; ⁵GBEM, Merck Serono Pharmaceutical R&D Co., Ltd., Beijing, China; ⁶Global Clinical Development Oncology, Merck Healthcare KGaA, Darmstadt, Germany; ⁷Global Patient Safety Innovation, Merck Healthcare KGaA, Darmstadt, Germany; ⁸Medical Oncology, Beaujon University Hospital, Clichy, France

Introduction: Tepotinib is a potent, highly-selective, oral MET inhibitor with antitumor activity and a manageable

safety profile in patients with solid tumors at the recommended phase II dose (RP2D; 500 mg once daily [QD]). Two phase Ib/II studies conducted in patients with advanced MET+ HCC met their primary efficacy endpoints; safety outcomes are reported. **Methods:** Two phase Ib/II studies conducted in Asian (1L; NCT01988493) and Western (2L; NCT02115373) patients with advanced HCC (ECOG performance status 0–1; Child-Pugh Class A; MET+ [Phase II only]). Asian patients received tepotinib at 300 mg, 500 mg or 1000 mg QD (Phase Ib), and either tepotinib (500 mg QD) or sorafenib (400 mg twice daily) (Phase II). Western patients previously treated with sorafenib received tepotinib (300 mg and 500 mg QD [Phase Ib]; 500 mg QD [Phase II]). Treatment was in continuous 21-day cycles. Treatment emergent adverse events (TEAEs) were graded by NCI CTCAE v4.03. **Results:** Across both studies, 121 patients (Asian:n = 59; Western:n = 62) received tepotinib 500 mg QD; median ages were 58 and 66 years and 90% and 84% were male, respectively. Asian and Western patients received tepotinib for up to 20.2 and 16.5 months (mean[SD], 4.8[5.1] and 3.5[3.0] months), respectively, and had similar TEAE profiles (Table). Peripheral edema was the most common TEAE (39.0% and 67.7%), treatment-related TEAE (Table) and treatment-related serious TEAE (3.4% and 3.2%); disease progression was the most common Grade ≥3 TEAE (12% and 14%) and TEAE

Table 1. Safety profiles for Asian and Western patients who received tepotinib 500mg QD (for Abstract no O-042)

Overall TEAE profile	Any cause TEAE, n (%)		Treatment-related TEAEs, n (%)	
	Asian* (n = 59)	Western* (n = 62)	Asian* (n = 59)	Western* (n = 62)
TEAE	59 (100)	60 (96.8)	47 (79.7)	52 (83.9)
Grade ≥3 TEAE	35 (59.3)	35 (56.5)	18 (30.5)	17 (27.4)
Serious TEAE	32 (54.2)	26 (41.9)	8 (13.6)	7 (11.3)
Treatment-related TEAEs	Any grade (10%#), n (%)		Grade 3 (%#), n (%)	
	Asian* (n = 59)	Western* (n = 62)	Asian* (n = 59)	Western* (n = 62)
Peripheral edema	14 (23.7)	23 (37.1)	0 (0)	5 (8.1)
Diarrhea	21 (35.6)	9 (14.5)	3 (5.1)	0 (0)
Fatigue	11 (18.6)	11 (17.7)	2 (3.4)	0 (0)
Decreased appetite	11 (18.6)	5 (8.1)	0 (0)	0 (0)
Nausea	5 (8.5)	9 (14.5)	0 (0)	0 (0)
Asthenia	0 (0)	13 (21.0)	0 (0)	0 (0)
Ascites	4 (6.8)	6 (9.7)	2 (3.4)	2 (3.2)
Blood creatinine increased	6 (10.2)	3 (4.8)	0 (0)	1 (1.6)
PPES	8 (13.6)	1 (1.6)	2 (3.4)	0 (0)
Increased lipase	4 (6.8)	4 (6.5)	3 (5.1)	3 (4.8)
Increased AST	5 (8.5)	2 (3.2)	2 (3.4)	2 (3.2)
Increased amylase	5 (8.5)	0 (0)	2 (3.4)	0 (0)
Hyperglycemia	2 (3.4)	1 (1.6)	2 (3.4)	0 (0)

* Final safety data from both phases of the study have been combined.

Incidence in either study. TEAEs are reported lower than the thresholds if their incidence met the threshold for either any grade or grade 3 treatment-related TEAEs.

AST, aspartate aminotransferase; l/t, leading to; PPES, Palmar-plantar erythrodysesthesia syndrome.

leading to death (5.1% and 8.1%) in Asian and Western patients, respectively, as reported by the investigator. Tepotinib doses up to 1000 mg QD were well tolerated and consistent with known safety profiles. **Conclusions:** Tepotinib was well tolerated in Asian and Western patients at the RP2D (500 mg QD). Doses up to 1000 mg QD tepotinib were well managed with no new safety signals.

O-043

Near-Infrared Photothermal/Photodynamic Therapy with Indocyanine Green for Hepatocellular Carcinoma Cells

Chikara Shirata¹, Junichi Kaneko¹, Yoshinori Inagaki¹, Takashi Kokudo¹, Takeaki Ishizawa¹, Nobuhisa Akamatsu¹, Junichi Arita¹, Norihiro Kokudo^{1,2}, Kiyoshi Hasegawa¹

¹The University of Tokyo, Japan, ²National Center for Global Health and Medicine, Japan

Background: Indocyanine green (ICG) is a photothermal agent, photosensitizer, and fluorescence imaging probe which shows specific accumulation in hepatocellular carcinoma (HCC) cells. We recently developed a photodynamic therapy (PDT) using ICG and near-infrared (NIR) laser as a new anti-cancer treatment for HCC. However, the molecular mechanism underlying this effect needs to be investigated. **Methods:** HuH-7 cells, a well-differentiated human HCC cell line, were transplanted subcutaneously into BALB/c-nu/nu mice for in vivo experiment. ICG was administered 24 h before NIR irradiation. The irradiation was performed with at three tumor locations for 3 min at each location by 823-nm NIR laser on days 1 and 7. HuH-7 tumor volume was monitored every 3 days. **Results:** The temperature of HuH-7 xenografts increased to 48.5 degrees celsius 3 minutes after ICG-NIR irradiation start. TUNEL analysis detected apoptosis in tumor tissue after ICG-NIR irradiation. Reactive oxygen species (ROS) production was detected after ICG-NIR irradiation both in vitro and in vivo. There was certain anti-tumor effect and ROS production even under cooling conditions. Repeated NIR irradiation increased the cell toxicity of ICG-NIR therapy; the mean tumor volume on day 9 was significantly smaller after ICG-NIR irradiation compared to tumor without irradiation (87 mm³ vs. 1332 mm³; p = 0.01) in HCC mice xenografts model. **Conclusions:** ICG-NIR therapy induced apoptosis in HCC cells via a photothermal effect and oxidative stress. Repeated ICG-NIR irradiation enhanced the anti-tumor effect.

O-044

The Multidisciplinary Treatment for Combined Hepatocellular-Cholangiocarcinoma. A Single Institution Experiences

Yoichi Miyata¹, Takazumi Tsunenari¹, Toru Kato¹, Toshimitsu Iwasaki¹, Takahiro Einama¹, Suefumi Aosasa², Yoji Kishi¹, Junji Yamamoto³

¹3rd Department of Surgery, National Defense Medical Collage Hospital, Japan, ²Department of Surgery, Shin-Kuki General Hospital, Japan, ³Department of Gastroenterological Surgery, New Tokyo Hospital, Japan

Background: Combined hepatocellular-cholangiocarcinoma (CHC) is known as a rare pathological type of primary liver cancer with poor prognosis. The benefit of multidisciplinary treatment has not been clear. **Patients and Methods:** Institutional chart review of the patients who underwent hepatectomy during the period between March 2008 and December 2018 was performed to select the patients with the diagnosis of CHC. How the patients were treated postoperatively and their long-term outcomes were reviewed. **Results:** Among 301 patients who underwent hepatectomy for primary liver cancer, 15 patients (5%) with CHC were selected. Median postoperative follow-up period was 24 months (8–62). Major hepatectomy was performed in 11 patients and limited resections in four patients. All but one patient with para-aortic lymph node metastases achieved R0 resection. The patient with R2 resection received postoperative chemotherapy with sorafenib. Another patient underwent left lobectomy with extra bile duct resection after response to gemcitabine-based chemotherapy for initially unresectable tumor and received postoperative chemotherapy with gemcitabine. According to the eighth edition of Union for International Cancer Control staging system, five patients were classified as stage IIIB and the other 10 patients as stage II. Tumor recurrence occurred in five patients during the observation period. The initial recurrence sites were liver in two patients, lung in one patient, pleura in one patient, and bilateral adrenal in one patient. Four patients received chemotherapy: one with gemcitabine, two with sorafenib and one patient with pleural metastases received radiation. Median survival period after recurrence was 13 months (3–27). One patient survived more than two years after recurrence with multidisciplinary treatment. Three patients achieved 5-year survival with two of them without recurrence. **Conclusion:** Our experience in 13 patients with CHC showed fairly good outcomes. Additional treatment even after recurrence might contribute to long survival in selected patients.

Molecular Pathogenesis and Pathology / Staging and Prognosis

O-045

Hepatitis B Virus Covalently Closed Circular DNA Levels in Para-Neoplastic Liver Tissues Independently Predict Postoperative Extrahepatic Metastasis and Overall Survival

Chau-Ting Yeh¹, Ming-Wei Lai¹, Chih-Lang Lin¹

¹Chang Gung Memorial Hospital, Taiwan

Background and Aims: New antiviral therapies against hepatitis B virus (HBV) are under vigorous development and focusing on elimination of liver cccDNA. However, the prognostic role of cccDNA in HBV-related hepatocellular carcinoma (HCC) patients has not been clearly defined. Recently, we developed a peptide nucleic acid (PNA)-clamping PCR method to provide a wider range of specific cccDNA quantification (up to 5 log of effective range). Here, we used this method to quantify cccDNA for outcome correlation. **Methods:** Extra-chromosomal DNA was extracted from para-neoplastic tissues using Hirt fractionation followed by PNA-clamping real-time PCR to quantify cccDNA. Totally 350 HBV-related HCC patients were included. Clinicopathological factors including immuno-histochemistry staining patterns of HBV surface antigen (HBsAg) and core antigen were reviewed. **Results:** It was found that cccDNA levels in para-neoplastic liver tissues ranged from 0 to 123.0 × 10(6) copies/gram. Linear regression analysis showed that liver cccDNA levels were positively

correlated with cirrhosis, HBeAg, serum HBV-DNA, tissue HBcAg expression, and nuclear HBcAg localization. Cox proportional hazard model analysis showed that cccDNA independently predicted overall survival (HR = 1.026 [1.007, 1.045], adjusted P = 0.006) and distant metastasis-free survival (HR = 1.025 [1.010, 1.040], adjusted P = 0.001), but not intra-hepatic recurrence free survival (P = 0.156). The prediction effect was independent of pre- or post-operative HBV-DNA levels or continuous usage of oral antiviral agents. On the other hand, presence of clustered staining pattern of HBsAg was found to be a strong independent predictor for intra-hepatic recurrence free survival (HR = 2.051 [1.492, 2.821], adjusted P < 0.001). **Conclusions:** Liver cccDNA was independently associated with postoperative overall survival and distant metastasis. In addition to oral antiviral treatment, further elimination of cccDNA might improve postoperative prognosis for HBV-related HCC patients.

O-046

Development of a Novel Prognostic Staging System in Combined Hepatocellular and Cholangiocarcinoma: PSM-CHCC Staging System

Xin Yin¹, Feng Zhang¹, Meng-Xin Tian¹, Ke-Shu Hu¹, Bei Tang¹, Jia Yuan¹, Yin-Hong Shi¹, Zheng-Gang Ren¹

¹Liver cancer institute, Zhongshan hospital, China

Background and Aims: Combined hepatocellular and cholangiocarcinoma (cHCC-CC) is a rare but increasingly recognized primary liver cancer, showing more aggressive

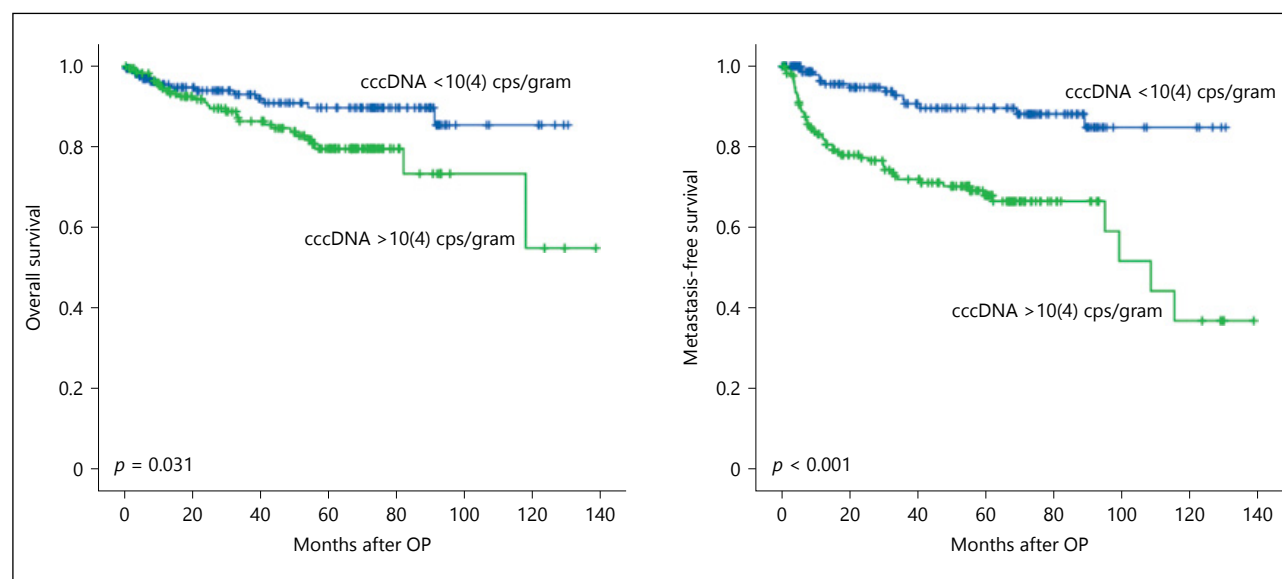


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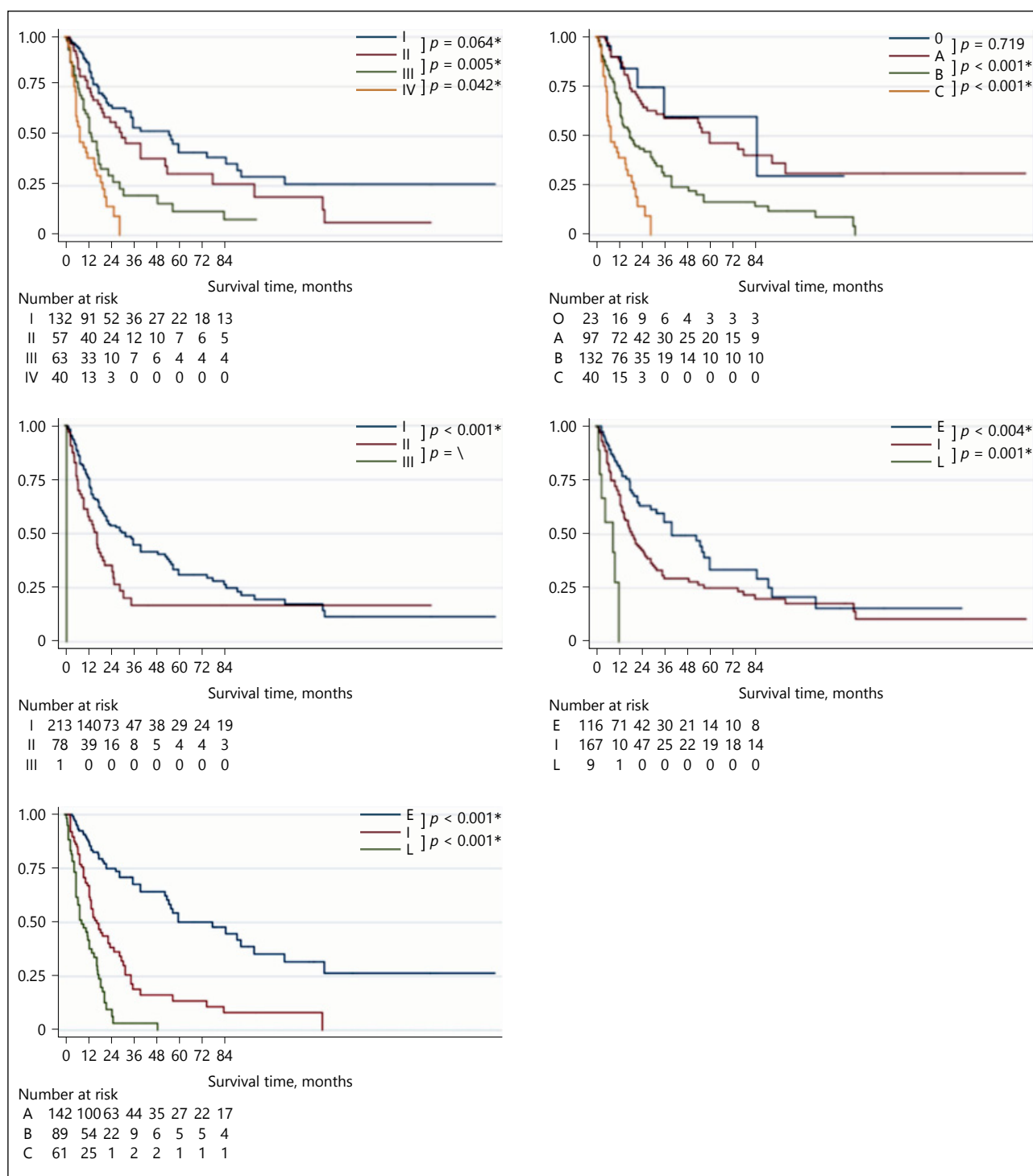


Fig. 1. (for Abstract no O-046).

behavior and worse outcome in comparison with hepatocellular carcinoma. Currently, no existing prognostic staging system is available for clinical utility in cHCC-CC. The aim of this study is to develop an effective and easy-to-use prognostic staging system specifically for cHCC-CC patients. **Methods:**

Between January 1993 and December 2015, a total of 292 patients pathologically diagnosed as Allen type C cHCC-CC were retrospectively included. Univariate and multivariate Cox regression analyses were adopted to identify the independent prognostic factors. A new prognostic staging model

for combined hepatocellular and cholangiocarcinoma (PSM-CHCC staging system) was developed and its predictive performance were verified in comparison with existing staging systems. **Results:** Using the scoring method based on the independent prognostic variables identified in present cohort, 292 CHCC-CC patients were subclassified into three subgroups according to the total score: A (scoring 0–2), B (scoring 3–4) and C (scoring ≥ 5), presenting significantly different median survival of 20.7, 14.0 and 8.0 months, respectively ($P < 0.001$). And multivariate analyses showed that the HR value of PSM-CHCC staging system was 2.7, with a higher C-index and AUC, and a lower AIC in comparison with the existing staging system based on discrimination efficacy analysis. All these results indicated that PSM-CHCC staging system possessed a potent capacity of prognosis prediction. **Conclusions:** The newly developed PSM-CHCC staging system outperformed other existing staging system, which can contribute to clinical decision making and prognostic prediction.

O-047

CircTUBD1 Acts as miR-146a-5p Sponge Affecting the Viability and Pro-Inflammatory Cytokine Production of Irradiated and LPS Stimulated Human Hepatic Stellate Cell Through TLR4 Signal Pathway

Hao Niu¹, Li Zhang¹, Yu-Han Chen², Zhao-Chong Zeng¹, Chia-Hsien Cheng³

¹Department of Radiation Oncology, Zhongshan Hospital, Fudan University, China, ²Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, China, ³Division of Radiation Oncology, Departments of Oncology, National Taiwan University Hospital, China

We aimed to identify the functions and mechanism of a new circular RNA circTUBD1 in irradiated and lipopolysaccharide (LPS) stimulated hepatic stellate cell (HSC) LX-2.

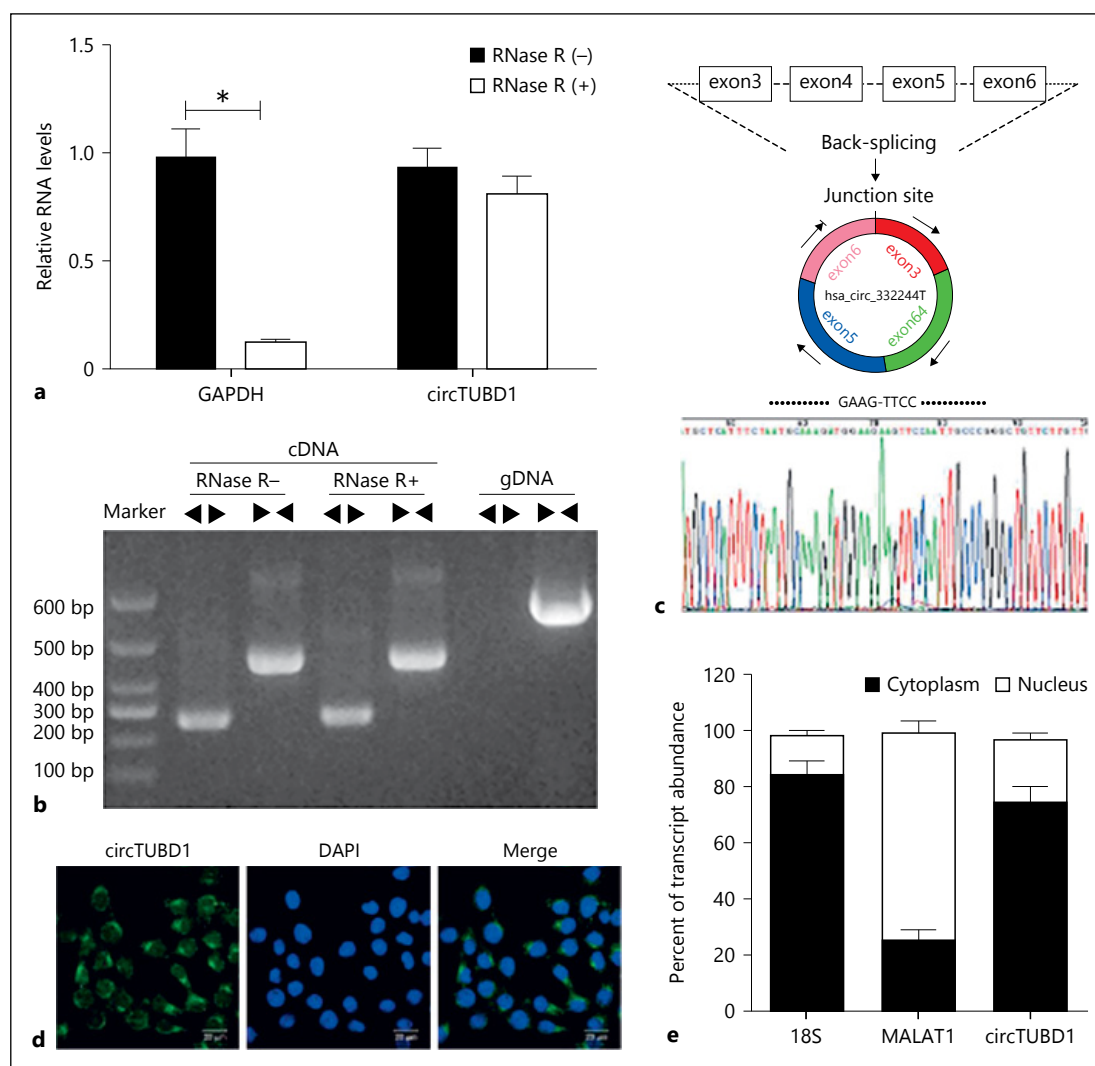


Fig. 1. (for Abstract no O-047).

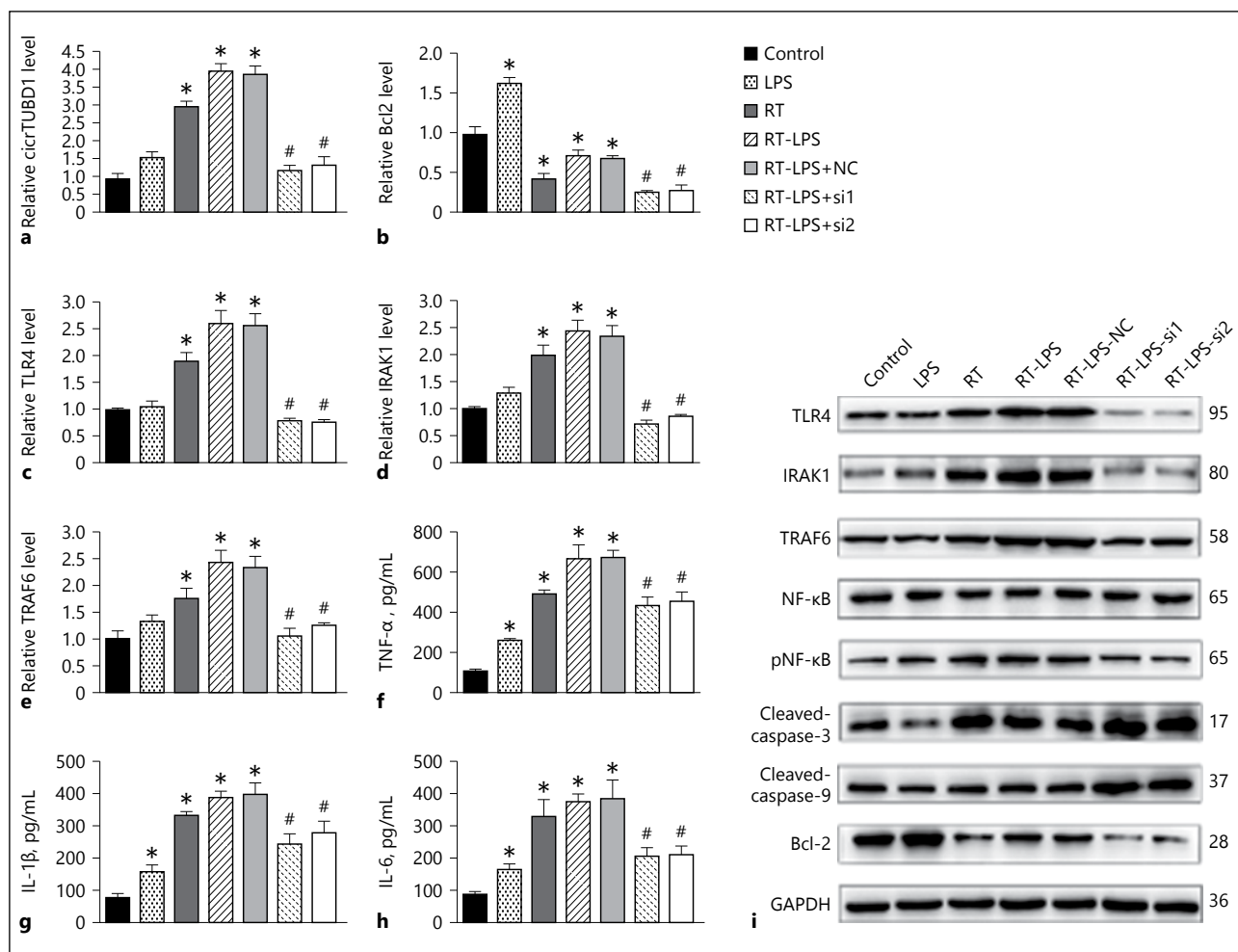


Fig. 2. (for Abstract no O-047).

CircRNAs are being identified as promising biomarkers for early diagnosis, prognosis, and therapy of human disease. Nevertheless, the expression profile and contribution of circRNAs in the development of radiation-induced liver disease (RILD) remain largely unknown. Our group found that the expression of circTUBD1 (hsa_circ_0044897) in irradiated and LPS stimulated the hepatic stellate cell (HSC) LX-2 cells was significantly up-regulated (Fold change 3.703683, $p < 0.004424$) compared with non-treated LX-2 cells analyzed by circRNA microarray and qRT-PCR. It was validated that circTUBD1 was more stable in LX2 cells and tissue than linear mRNA verified by RNase R digestion treatment and Sanger sequencing. To explore the functions of circTUBD1, short interfering RNAs (siRNAs) targeted to circTUBD1 were designed. We found that the silencing of circTUBD1 inhibited the proliferation of LX-2 by CCK8 and colony formation assay and promoted apoptosis of LX-2 cells detected by flow cytometry. The level of pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α were significantly decreased by knocking down of circTUBD1 through suppressing the transduction of

TLR4 signal pathway in LX-2 cells under the stimulation of irradiation and LPS. Bioinformatics software, dual luciferase reporter assay, and RNA pull-down assays together verified that miR-146a-5p was significant enrichment by circTUBD1 probes. Fluorescence in situ hybridization (FISH) demonstrated that most of circTUBD1 and miR-146a-5p were co-localized in the cytoplasm. A series of rescue assays by co-transfection proved that circTUBD1 could partly reverse the effect of miR-146a-5p on the viability and pro-inflammatory cytokine production of irradiated and LPS stimulated LX-2 cells via TLR4 signal pathway by acting as miR-146a-5p sponge. CircTUBD1 may serve as a novel therapy target for RILD.

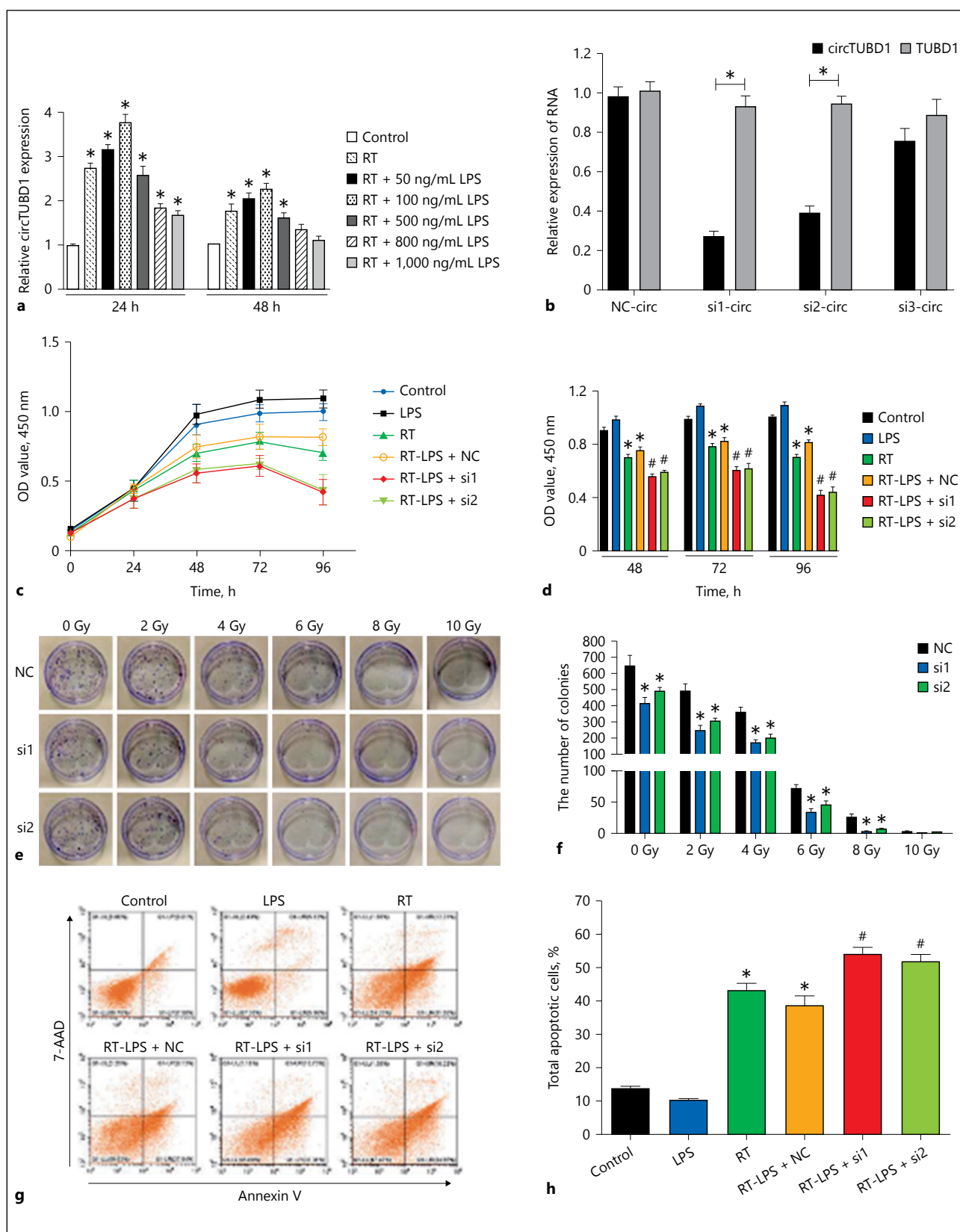


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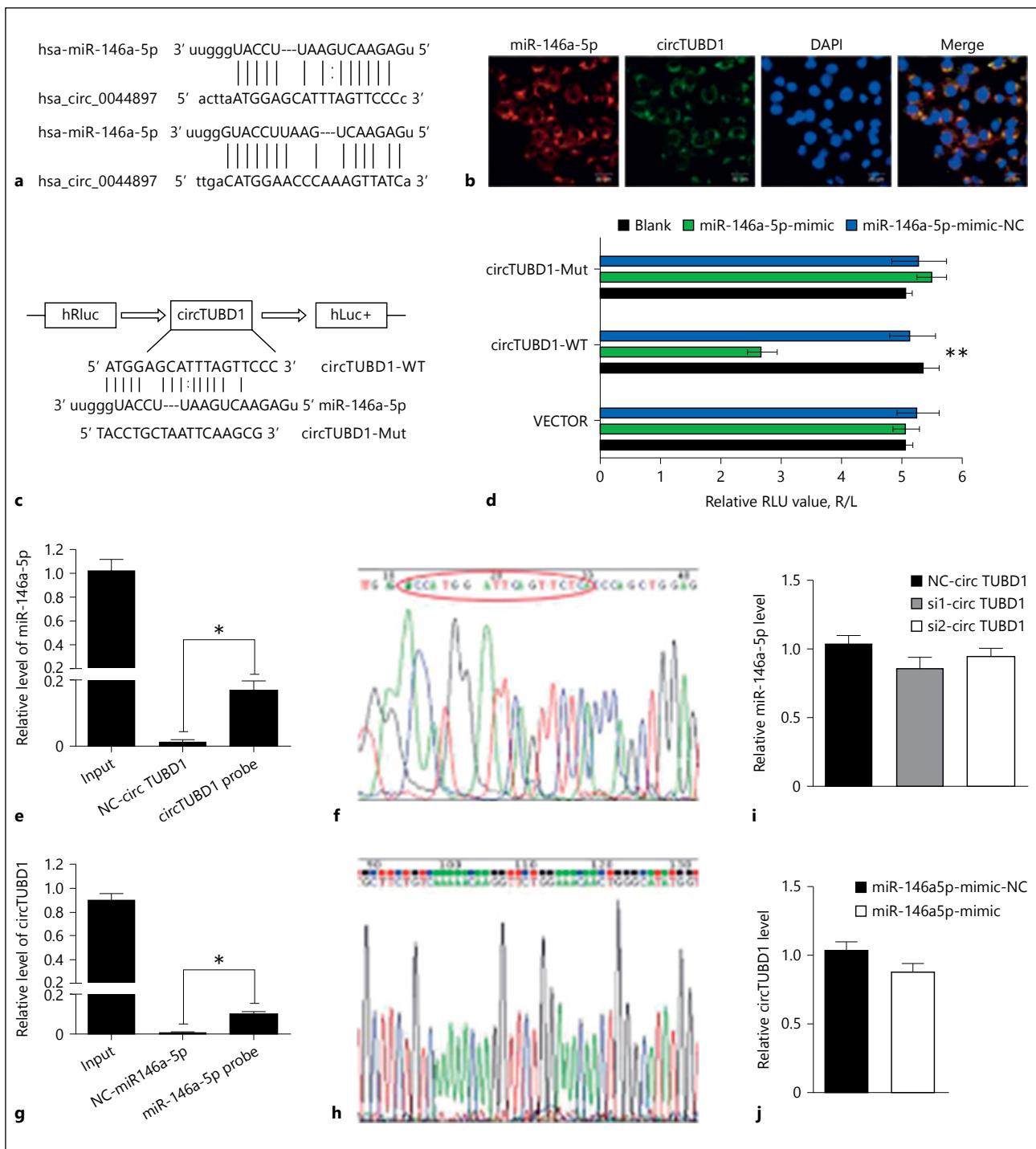


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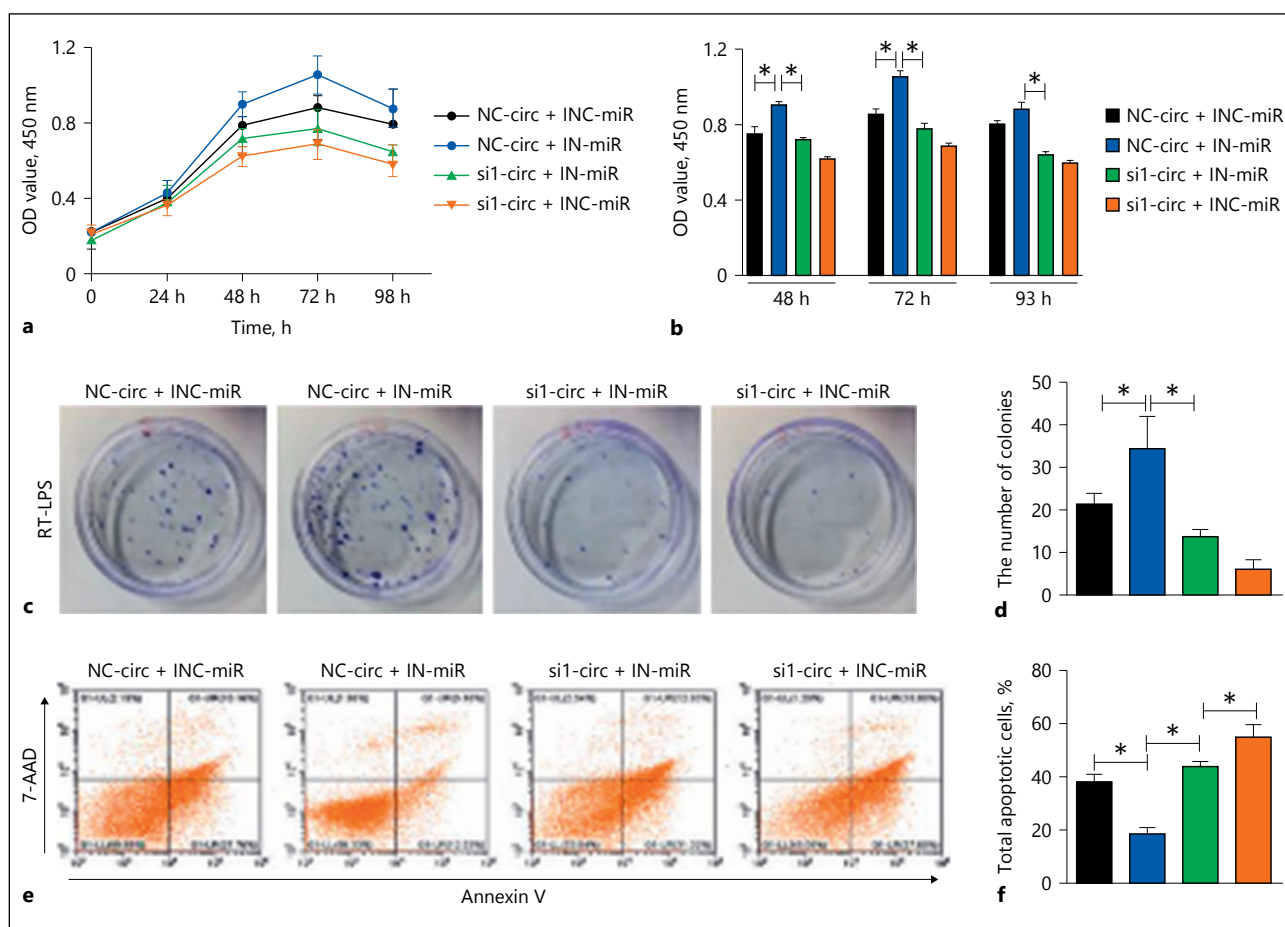


Fig. 5. (for Abstract no O-047).

O-048

Circulating Neutrophils Promote HCC Progression by STAT3 and P53 Signal Pathway

Yan Wang¹, Rongrong Yao², Lan Zhang¹, Zhenggang Ren¹

¹Liver Cancer Institute, Zhongshan hospital, Fudan University, China, ²Department of Internal medicine, Shanghai General Hospital, Jiaotong University, China

Background: Tumor associated neutrophils (TANs) contribute to tumor progression, invasion and angiogenesis. However, most studies of TANs focused on tumor infiltration neutrophils, little was known about the roles of circulating neutrophils in tumor development. This study was aimed to verify the pro-tumor effects of circulating neutrophils and its' mechanism in HCC. **Methods:** The clinical data of 127 patients with HCC underwent TACE were collected, the prognostic factors of overall survival for them were analyzed by Kaplan Meier curve and Cox models. Circulating neutrophils of HCC patients were sorted and cocultured with human HCC cell lines

MHCC97H and SMMC7721, then tumor cell proliferation, migration and invasion were detected by CCK8, scratch tests and transwell tests. Phosphokinase array was used to determine the kinase profile of MHCC97H and SMMC7721 cultured with or without circulating neutrophils. **Results:** The result of multivariate analyses of 127 patients showed that increased circulating neutrophils was an independent poor prognostic factor for OS of HCC patients underwent TACE. After cocultured circulating neutrophils with HCC cell lines, we demonstrated that circulating neutrophils promoted migration and invasion of HCC cell lines, but no effect on proliferation. We analyzed a phosphokinase array on HCC cell lines cultured with or without circulating neutrophils to determine the kinase profile of several distinct signaling pathways. It showed that p-P53S46 and p-STAT3Y705 were up-regulated after cocultured with circulating neutrophils. Then we treated HCC cell lines with inhibitors of P53 or STAT3, repeated scratch tests and transwell tests showed the promotion effect on migration and invasion of circulating neutrophils were reversed. **Conclusion:** Circulating neutrophils was an independent poor prognostic factor for OS of HCC patients underwent TACE, it had pro-tumor effect on HCC through P53 and STAT3 pathway.

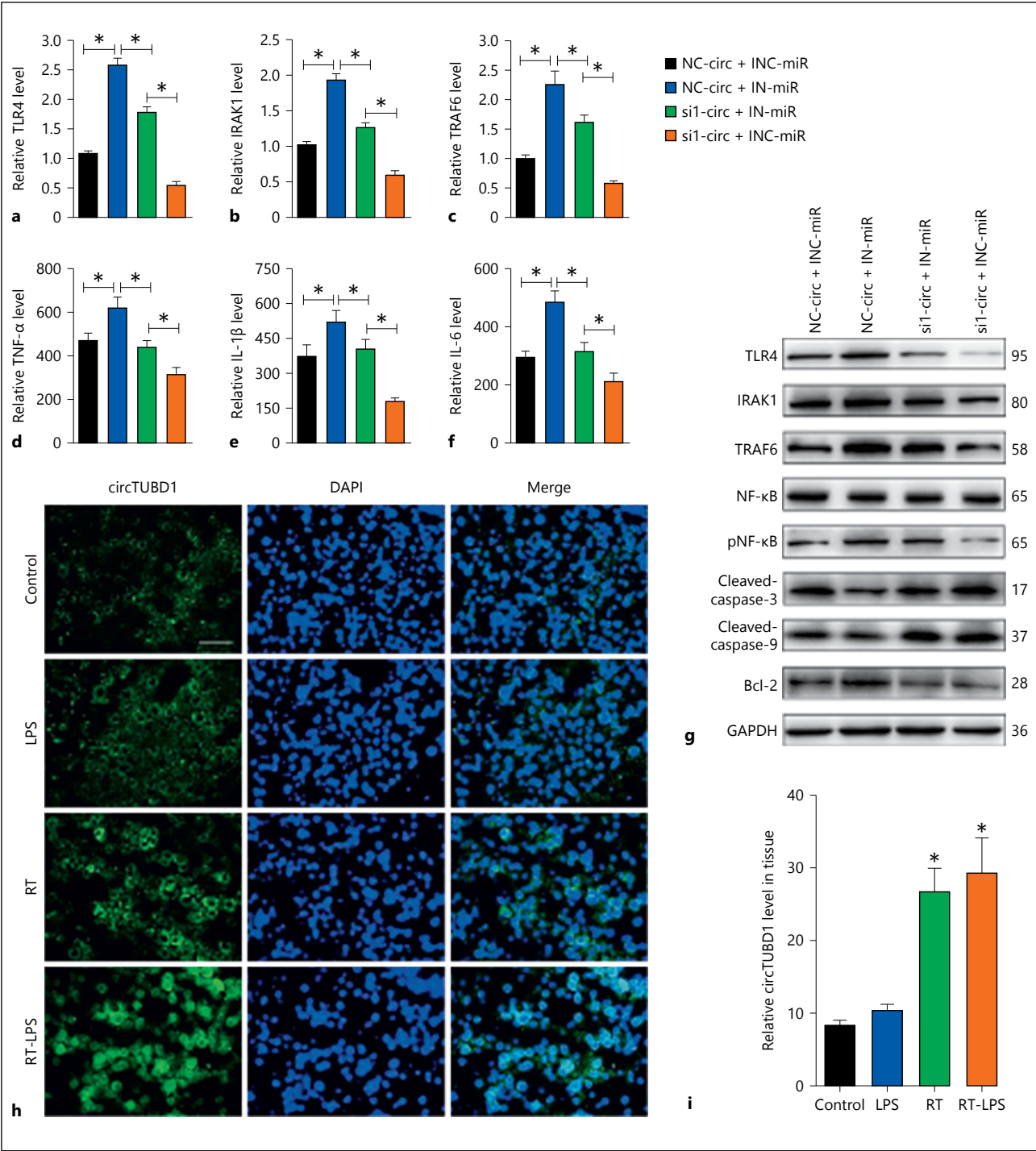


Fig. 6. (for Abstract no O-047).

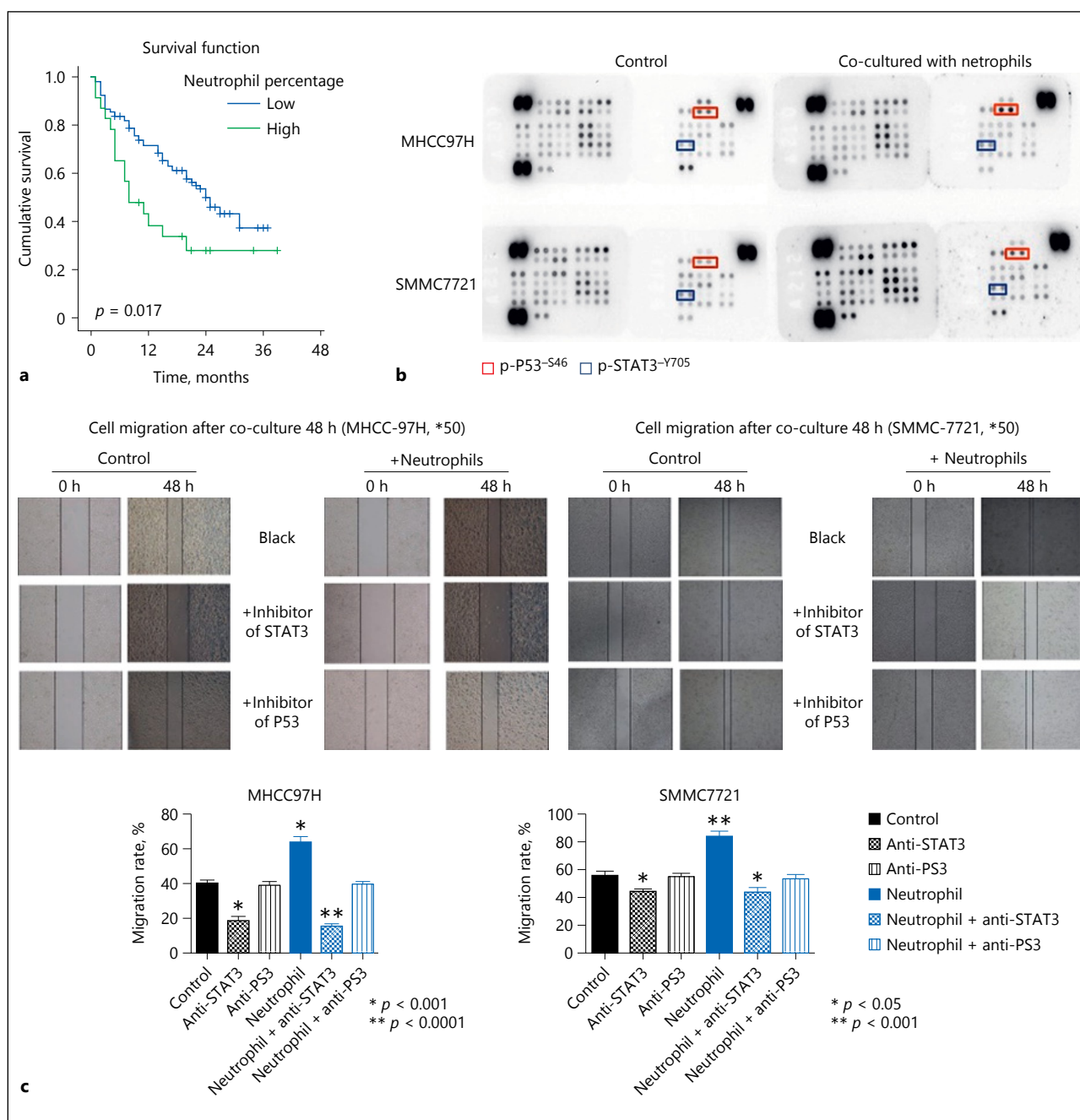
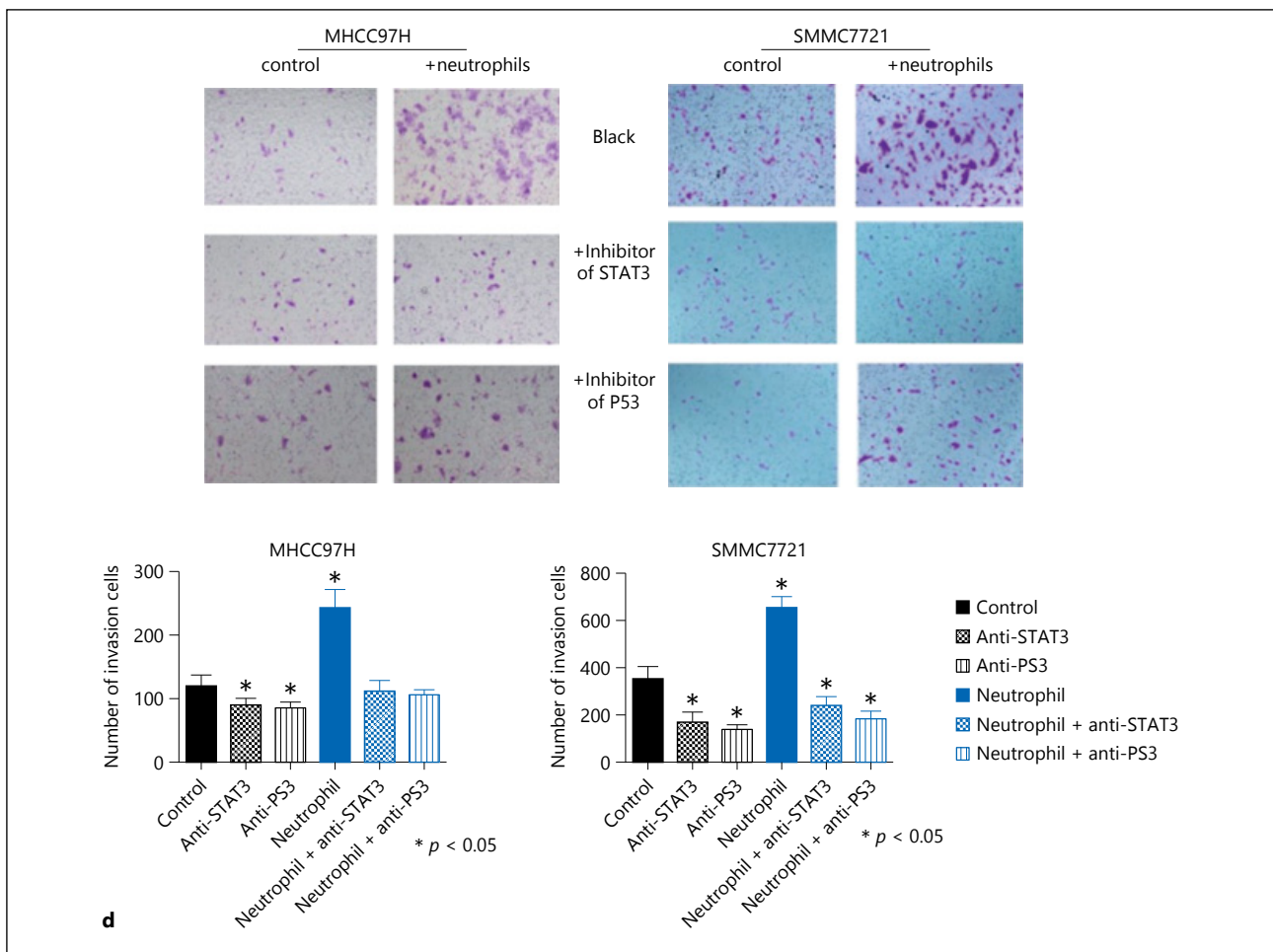


Fig. 1. a Survival curves of different groups: os for low circulating neutrophil group was 22.92 months, while os for high circulating neutrophils group was 16.25 months (HR = 1.9, 95% CI: 1.086–3.325). **b** Phosphokinase array on HCC cell lines cultured with or without circulating neutrophils: p-P53546 and p-STAT3Y705 were up-regulated after co-cultured with circulating neutrophils both in MHCC-97H and SMMC-7721 cell lines. **c, d** Migration and invasion of HCC cell

lines after co-cultured with circulating neutrophils and treated with inhibitors of P53 and STAT3: cell migration rates (**c**) and number of invasion cells (**d**) of MHCC-97H and SMMC-7721 were up-regulated after co-cultured with circulating neutrophils, but the promotion effect on migration and invasion of circulating neutrophils were reversed when treated with inhibitors of PS3 or STAT3 (for Abstract no O-048).

(Figure continued on next page.)



Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy

O-049

Subsequent Anticancer Medication Following First-line Lenvatinib: Post Hoc Responder Analysis From the Phase 3 REFLECT Study in Unresectable Hepatocellular Carcinoma

Angel Alsina¹, Masatoshi Kudo², Arndt Vogel³, Ann-Lii Cheng⁴, Won Young Tak⁵, Baek-Yeol Ryoo⁶, T.R. Jeffry Evans⁷, Carlos Lopez Lopez⁸, Bruno Daniele⁹, Soamnauth Misir¹⁰, Min Ren¹⁰, Namiki Izumi¹¹, Shukui Qin¹², Richard S. Finn¹³

¹Tampa General Hospital, USA, ²Kindai University Faculty of Medicine, Japan, ³Hannover Medical School, Germany, ⁴National Taiwan University Hospital and National Taiwan University Cancer Center, Taiwan,

⁵School of Medicine, Kyungpook National University, Korea, ⁶Asan Medical Center, University of Ulsan College of Medicine, Korea, ⁷University of Glasgow, Beatson West of Scotland Cancer Centre, UK, ⁸Marques de Valdecilla University Hospital, Spain, ⁹Ospedale del Mare, Italy, ¹⁰Eisai Inc., USA, ¹¹Musashino Red Cross Hospital, Japan, ¹²Nanjing Bayi Hospital, China, ¹³Geffen School of Medicine, UCLA Medical Center, USA

Background: Lenvatinib (LEN) was shown to be noninferior to sorafenib (SOR) for median overall survival (mOS, 13.6 vs 12.3 months; HR 0.92; 95% CI 0.79–1.06). LEN was superior vs SOR for secondary end points including objective response rate (ORR) per mRECIST: 24.1% vs 9.2% by investigator and 40.6% vs 12.4% by independent review (Kudo, *Lancet*, 2018). We report a post hoc analysis of responders who received post-progression anticancer medication during survival follow up. **Methods:** In REFLECT, patients with unresectable hepatocellular carcinoma were randomized (1:1) to first-line LEN or SOR. Objective response was complete or partial response (mRECIST per investigator). Patients discontinuing treatment following progression were followed for survival every 12 weeks; subse-

quent anticancer medication was recorded until death. Data cutoff: November 13, 2016. mOS was calculated using Kaplan-Meier estimates with 2-sided 95% CIs. **Results:** 1/3 of the overall study population (156/478 patients randomized to LEN and 184/476 to SOR) received subsequent anticancer medication, most commonly SOR (25% in LEN arm). ECOG performance status and laboratory assessments, including liver function tests, were comparable between arms before subsequent treatments. Among these patients, mOS was 21 vs 17 months and ORR was 27.6% vs 8.7% for LEN vs SOR arms, respectively. Among responders who received post-progression anticancer medication the mOS (95% CI) was 26 months (18.5–34.6) for LEN (n = 43) and 22 months (14.6–NE) for SOR (n = 16). For LEN responders who subsequently received SOR (n = 35), mOS was 26 months (95% CI 18.2–34.6). **Conclusions:** In REFLECT, 1/3 of patients randomized to first-line LEN received subsequent anticancer medication, including SOR, with an mOS of 21 months. In this exploratory, post hoc analysis of patients who responded to LEN and received any subsequent anticancer medication, including SOR, mOS was 26 months.

O-050

Drug-Eluting Beads Versus Conventional Chemoembolization for the Treatment of Unresectable Hepatocellular Carcinoma with Extrahepatic Collateral Blood Supply

Sung-hua Chiu¹, Wei-Chou Chang¹, Chang-Hsien Liu¹, Yu-Lueng Shih², Hsuan-Hwai Lin², Chih-Yung Yu¹, Guo-Shu Huang¹, Hsian-He Hsu¹

¹Department of Radiology, Tri-Service General Hospital, Taiwan, Taiwan, ²Department of Internal Medicine, Tri-Service General Hospital, Taiwan, Taiwan

Aims: To compare the outcome and complications of unresectable hepatocellular carcinoma (HCC) with extrahepatic collateral (EHC) blood supply treated by either drug-eluting beads (DEB) or conventional transarterial chemoembolization (c-TACE). **Methods:** We performed a retrospective review of 575 patients with unresectable HCC who received TACE treatment in our hospital from January 2016 to March

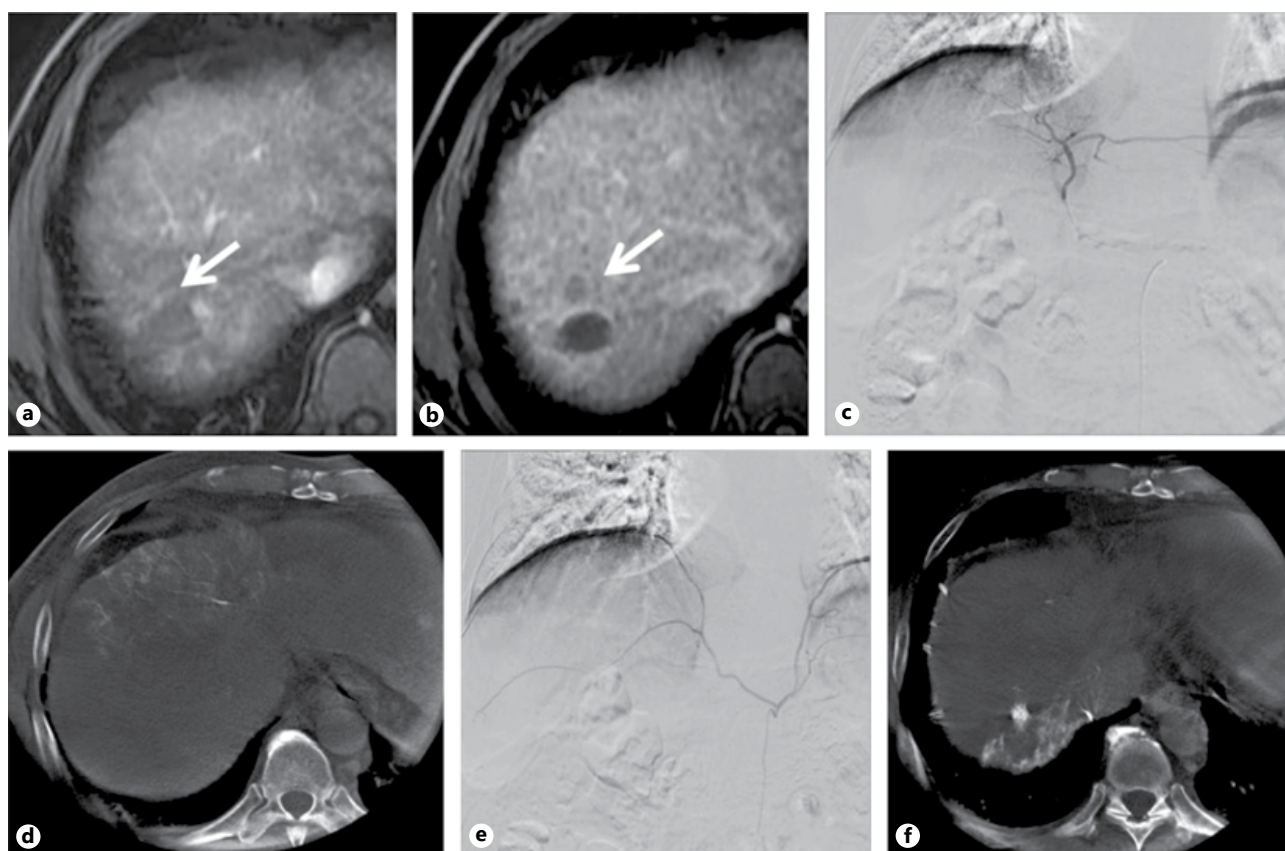


Fig. 1. a, b MRI study performed before TACE showed three nodules (arrow) abutting the former ablation lesion with early arterial enhancement (a) and washout in delayed phase (b), consistent with recurrent HCCs. (c–f) The digital subtraction angiography of middle hepatic artery (c) and right inferior

phrenic artery (e) revealed superimposed territories, and the contrast-enhanced cone beam CT of middle hepatic artery (d) and right inferior phrenic artery (f) can help interventional radiologists to discern overlapping territories, leading to accurate embolization (for Abstract no O-050).

2019. Among them, 61 patients (50 men and 11 women with mean age of 63.4 years) had EHC blood supply and were separated into two groups: DEB-TACE ($n = 42$) and c-TACE ($n = 19$). We recorded the demographics and laboratory data, baseline imaging characteristics, digital subtraction angiography (DSA) and cone beam CT (CBCT) images during angiography, types of EHC arteries, and the incidence of liver dysfunction, post-embolization syndrome and major complications. Kaplan-Meier method with Breslow test was used to compare the survival outcomes. **Results:** During angiography, CBCT had a higher sensitivity in detecting HCC lesions supplied by EHC arteries compared to DSA alone (16.12% versus 6.61%; $p = 0.0000$). Right inferior phrenic artery (RIPA) was the most common EHC arteries (73.75%). Our results in favor of DEB-TACE was a better safety profile with significant decrease in incidence of liver dysfunction ($p = 0.044$), while the incidence of post-embolization syndrome and major complications was comparable in two groups ($p = 0.11$). Among these EHC arteries, RIPA had a significantly lower risk of complications than other EHC arteries (8.16% versus 41.67%; $p = 0.011$). The overall survival (OS) was significantly longer for patients who had undergone DEB-TACE compared to the c-TACE group (17.61 months versus 12.43 months; $p = 0.039$). **Conclusions:** DEB-TACE is a safe and effective treatment for HCC with EHC blood supply. With the aid of CBCT, DEB-TACE can significantly improve OS than c-TACE.

O-051

Prognosis of Radiofrequency Ablation for Hepatocellular Carcinoma with BCLC Early and Intermediate Stage: A Real World Study in a Single Center with 1783 Series Patients

Zhenggang Ren¹, Lan Zhang¹, Bei Tang¹, Hui Ma¹, Xin Yin¹, Rongxin Chen¹

¹Department of Hepatic Oncology, Liver Cancer Institute, Zhongshan Hospital, Fudan University, China

Background: Radiofrequency ablation (RFA) has been accepted as first line option for small liver cancer and also used for some patients with extended criteria such patients with intermediated stage in combination with transcatheter arterial chemoembolization. **Method:** During 2000 to 2016 there were 1783 treatment naive patients with BCLC stage 0, A and B patient were treated RFA in Department of Hepatic Oncology, Zhongshan Hospital, Fudan University. The 5-year and 10-year overall survival were evaluated with Kaplan-Meier method. Univariate and multivariate analysis were carried out for prognostic factors identification. **Results:** Among the 1783 patients there were 1522 (85.4%), 25 (1.4%), 65 (3.5%) and 174 (9.8%) with HBV, HCV, HBV plus HCV, non HBV non HCV etiologic background. There were 456 (25.6%), 1084 (60.8%), 243 (13.6%) with BCLC stage 0, A, B and 1643 (92.1%), 140 (7.9%) with Child-Pugh A, B, respectively. The 5-year and 10-year

overall survival were 65.0% and 38.9%; 53.2% and 25.0%; 37.5% and 20.1% in BCLC 0, A, B, respectively. There were 1046 (57.8%) underwent TACE either for in combination or recurrent. Multivariate analysis revealed that up to 6 criteria (largest tumor diameter plus tumor nodule number), alpha-fetoprotein levels, BCLC stages and Child-Pugh class were independent prognostic factors. **Conclusion:** long term survival can be achieved for early stage HCC with comparable outcomes to surgery options. RFA could be used to treat intermediate stage HCC with favorable 5-year survival. Up to six criteria could be used as prognostic factor for RFA treatment.

O-052

Predictors of Three Months Survival Hepatocellular Carcinoma Patients who Underwent Transarterial Chemoembolization

Ulfa Kholili¹, Annisa Zahra Mufida¹,
Frida Lorita Pitoyo¹, Herry Purbayu¹,
Titong Sugihartono¹, Ummi Maimunah¹,
Iswan abbas Nusi¹, Poernomo Boedi Setiawan¹

¹Airlangga University, Indonesia

Background: TACE is paliative therapy that recommended for intermediate stage HCC. Evaluation of three months survival HCC after TACE procedure is important to decide whether re-TACE or other treatment. **Objective:** To determine factors as predictor of survival HCC patients in 3 months after TACE procedure at Dr. Soetomo General Hospital. **Material and Method:** All subjects were HCC patients with BCLC stage B who underwent TACE from at Dr. Soetomo General Hospital. The independent variables were tumor size (≥ 10 cm), AFP level (≥ 400 ng/mL), Bilirubin (≤ 1 mg/dL), albumin (≥ 3 mg/dL) level and FIB-4 score > 3.25 . As dependent variable is 3 months survival. Statistics of predictor survival using multivariate analysis cox regression. Survival analysis use Kaplan-meier curve. **Result:** This study involved 110 subjects consist of 86% men and 21.8% women with average of 52.15 y.o, most of HCC etiology was chronic hepatitis B (64,5%). Subjects consist of child-pugh score A and B in same proportion (50% and 50%) with tumor size 11.80 cm, AFP level 644.58 ng/mL, albumin level 3.51 mg/dL, total bilirubin 1.29 mg/dL, and FIB-4 score 3.77. The Incidence rate of survival in 3 months observation was 61,8%. In univariate analysis, only AFP and bilirubin level had a significant difference with $p = 0.000$ and $p = 0.048$ in three-month survival HCC after TACE procedure despite failure to be independent predictor based on multivariate analysis. **Conclusion:** Tumor size, AFP, bilirubin, albumin and FIB-4 score was not found to be significant independent predictors of three months survival HCC patients after TACE procedure.

O-053

Long-Term Outcomes of No-Touch Multibipolar versus Monopolar Radiofrequency Ablation for Cirrhotic Patients with Treatment Naïve Hepatocellular Carcinoma ≤ 4 cm: A Multicenter Study

Sheng-Wei Cheng¹, Li-Wei Wu¹, Yen-Cheng Chiu³, Ming-Shun Wu^{1,2}

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Municipal Wan-Fang Hospital, Taipei Medical University, Taipei, Taiwan, ²Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ³Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Cheng-Kung University Hospital, Tainan, Taiwan, Taiwan

Background: Multibipolar RF electrodes enable no-touch method for tumor ablation. Long-term comparison between no touch multibipolar RF ablation and monopolar RF ablation remains unclear. **Aim:** This multicenter retrospective study, long-term outcomes of these two ablation methods for HCC ≤ 4 cm were compared. **Methods:** From 2010 to 2017, 385 cirrhotic patients with new HCC were enrolled. The maximal tumor size was 4 cm and the maximal tumor number was three. After propensity score matching, 234 patients with 331 tumors were enrolled. Two to five Celon bipolar and one Cool tip electrode were used with percutaneous approach. **Results:** Complete ablation rate were 98.2% and 77.6% for bipolar and monopolar group, respectively. Monopolar method and tumor size > 2 cm were the two predictive factors for incomplete ablation. After a median follow-up of 2.14 years, 1 year 3 year 5 year local recurrence rate were 4.2% 5.7% 5.7% for the no

touch group and 30.0% 41.3% 41.3% for the monopolar group. Safety margin less than 5 mm, monopolar method and tumor abutting vessel > 3 mm were three significant factors for local tumor progression. The 1 year 3 year 5 year distant recurrence rate were 12.8% 24.9% 35.9% and 36.3% 57.3% 65.6%, respectively. Tumor number more than one and safety margin less than 5 mm and monopolar method were the three main factors contributing to distant recurrence. The 1 year 3 year 5 year overall survival were 93.6% 84.8% 65.3% and 91.3% 70.3% 58.0%, respectively. Child Pugh B disease was the most significant factor for poor overall survival. **Conclusion:** No-touch multibipolar RF ablation provide better disease free survival. Child Pugh B disease is the most significant factor affecting overall survival.

O-054

Stratification using Artificial Neural Network for Portal Vein Invaded Hepatocellular Carcinoma Treated with Transarterial Chemoembolization Monotherapy

Bin-Yan Zhong¹, Lei Zhang¹, Xiao-Li Zhu¹, Jing-Jing Song², Jian-Song Ji², Cai-Fang Ni¹

¹The First Affiliated Hospital of Soochow University, China, ²Zhejiang University Lishui Hospital, The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui Central Hospital, China

Objectives: We aimed to establish a prognostic prediction model to determine who will benefit from transarterial chemoembolization (TACE) monotherapy for patients with hepatocellular carcinoma (HCC) invading the portal vein. **Materials and Methods:** HCC patients with portal vein invasion and treated with TACE monotherapy at hospital A between January 2008 and May 2018 as training cohort and hospital B between May 2012 and May 2018 as validation cohort were included. In training cohort, independent risk factors associated with overall survival (OS) were identified by univariate and multivariate Cox proportional hazards analysis. Afterwards, a prognostic prediction model was established to find out who will benefit most from TACE monotherapy. The accuracy of the prediction model was validated in validation cohort. **Results:** 242 patients (training cohort: n = 159; validation cohort: n = 83) from two centers were included. The median OS was 7.1 months in training cohort and 8.5 months in validation cohort, respectively. In training cohort, the prognostic prediction (PP) model was established based on the following five independent risk factors: Cheng's Classification (0 if type I, 3 if type II, 5 if type III), Eastern Cooperative Oncology Group score (0 if 0, 3 if 1), maximum tumor size (2 if < 5 cm, 4 if 5–10 cm, 6 if > 10 cm), number of HCC nodules (3 if 1, 6 if > 1), and Child-Pugh stage (3 if A, 6 if B7). PP score of 17.5 was identified as cut-off point and patients were divided into two groups by PP score < 17.5

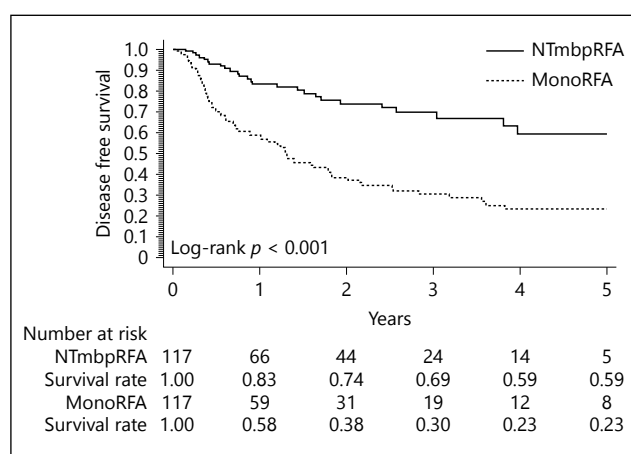


Fig. 5. Disease-free survival comparison with Log-rank test (for Abstract no O-053).

and >17.5 in survival benefit and prognostication (8.8 vs. 5.5 months; $P < 0.001$). The PP model received high accuracy with C-index of 0.827 when validated in validation cohort. **Conclusions:** Portal vein invaded HCC patients with PP score <17.5 may benefit most from TACE monotherapy.

Treatment: Systemic, Targeted, Novel Target or Experimental Therapy

O-055

Efficacy and Safety of Ramucirumab (RAM) in Asian and Non-Asian Patients with Advanced Hepatocellular Carcinoma (HCC) and Elevated Alpha-Fetoprotein (AFP): Subgroup Analysis from Two Randomized Studies

Takuji Okusaka^{1,2}, Yoon-Koo Kang¹, Masatoshi Kudo², Ho-Yeong Lim³, Chih-Hung Hsu⁴, Arndt Vogel⁵, Giovanni Brandi⁶, Rebecca Cheng⁷, Iris Carton⁸, Paolo Abada⁹, Yanzhi Hsu⁹, Andrew Zhu¹⁰, Chia-Jui Yen¹¹

¹Asan Medical Center, University of Ulsan, Korea,

²Kindai University, Japan, ³Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea, ⁴National Taiwan University Hospital, Taiwan, ⁵Hannover Medical School, Germany, ⁶University of Bologna, Italy, ⁷Eli Lilly and Company, Taiwan, ⁸Eli Lilly and Company, Belgium, ⁹Eli Lilly and Company, USA, ¹⁰Massachusetts General Hospital Cancer Center, Harvard Medical School, USA, ¹¹National Cheng Kung University, Taiwan, ¹²National Cancer Center Hospital, Japan

Background: The etiological factors and management of HCC vary by geographical region. REACH-2 and REACH3 showed significant survival benefits of RAM treatment for HCC in patients (pts) with baseline AFP ≥ 400 ng/mL. We conducted a pooled subgroup analysis to investigate the efficacy and safety of RAM in Asian and non-Asian pts from REACH-2 and REACH (high AFP subpopulation). **Methods:** Pts were randomized to receive RAM 8 mg/kg IV or placebo (PL) once every two weeks, plus best supportive care, until disease progression or unacceptable toxicity. Endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety. Kaplan-Meier analysis and Cox proportional hazards regression were performed for OS and PFS. Efficacy analyses were stratified by study. **Results:** Across the two studies, 291 Asian pts were randomized to RAM (168) or PL (123); 251

Table 1. (for Abstract no O-055)

Analysis Population (RAM v PL)	Asian N = 291 (RAM 168, P 123)	Non-Asian N = 251 (RAM 148, P 103)
OS median, month	8.08 v 4.76	7.98 v 5.22
HR (95% CI)	0.73 (0.56, 0.95)	0.65 (0.49, 0.86)
PFS median, month	2.73 v 1.45	3.06 v 1.87
HR (95% CI)	0.58 (0.44, 0.76)	0.55 (0.41, 0.73)
ORR, %	4.2 v 0.8	6.8 v 1.0
DCR, %	53.6 v 33.3	59.5 v 41.7

non-Asian pts were randomized to RAM (148) or PL (103). Baseline characteristics were generally balanced between treatment arms in Asian and non-Asian pts. RAM significantly improved median OS and PFS in both Asian pts and non-Asian pts (Table). The results of ORR and DCR are shown in the table. The most common grade ≥ 3 adverse event occurring in the RAM arm of Asian and non-Asian pts was hypertension (7.7% and 16.9%, respectively). **Conclusion:** This subgroup analysis demonstrates survival benefits of RAM treatment in Asian and non-Asian patients with advanced HCC and AFP ≥ 400 ng/mL. Treatment was well tolerated, with similar safety profiles between Asian and non-Asian pts.

References

- 1 Fong et al. Cancer 2014;120:2824–38.
- 2 Zhu et al. J Clin Oncol 2018;36:suppl. abstr 4003.
- 3 Zhu et al. Lancet Oncol 2015;16:859–70 Previously presented at ESMO Asia 2018 Congress, FPN 1490, Kang YK et al. Reused with permission.

O-056

The Efficacy and Safety of Lenvatinib in Patients with HBV Related Hepatocellular Carcinoma: A Real World Practice in China

Lan Zhang¹, Yi Chen¹, Ningling Ge¹, Yanhong Wang¹, Rongxin Chen¹, Zhenggang Ren¹

¹Liver Cancer Institute, Zhongshan Hospital, Fudan University, China

Background: Lenvatinib (LEN) has been approved as first-line agent for unresectable hepatocellular carcinoma (uHCC). However, following the introduction of LEN in clinical practice in China in september 2018, the drug has been used not only in TKI naive but also in TKI experienced patients as second- or third-line treatment, and therapeutic response and adverse events (AEs) in HBV-related HCC also have not been elucidated. This study aimed to investigate the efficacy and safety of LEN for HBV-related uHCC in the real-world setting. **Methods:** HBV-related uHCC patients who administered LEN

Table 1. Efficacy (for Abstract no O-056)

	One month			Three month		
	Total (n = 26)	TKI naive (n = 10)	TKI experienced (n = 16)	Total (n = 16)	TKI naive (n = 6)	TKI experienced (n = 10)
CR	0	0	0	0	0	0
PR	19.2% (5)	20% (2)	18.8% (3)	50% (8)	50% (3)	50% (5)
SD	50% (13)	30% (3)	62.5% (10)	25% (4)	33.3% (2)	20% (2)
PD	30.8% (8)	50% (5)	18.7% (3)	25% (4)	16.7% (1)	30% (3)
ORR	19.2%	20%	18.80%	50%	50%	50%
OCR	69%	50%	81.2%	75%	83.3%	70%

The efficacy of LEN was evaluated by mRECIST criteria after one and three month since the first time using LEN. CR, complete response; PR, partial response; SD, disease stable; PD: disease progression; ORR, objective response rate; DCR: disease control rate.

Table 2. AFP Response Rate (for Abstract no O-056)

Time	AFP response rate
1M	50% (9/18)
3M	58.3% (7/12)

AFP positive >20 ng/ml) patients (n = 30) was include, of which 18 patients were available for analysis at one month follow up, and 12 patients were available at three month follow up.

Table 3. Key function (for Abstract no O-056)

	1 m (n = 31)	3 m (n = 17)
Improved	3.2% (1)	5.9% (1)
Stable	90.3% (28)	88.2% (15)
Worsen	6.5% (2)	5.9% (1)
>7	0	0

Child-pugh score was used to evaluate the liver function. Improved means decrease of score. Worsen means increase of score baseline score was used as control.

Table 4. Treatment related AEs of lenvatinib (for Abstract no O-056)

	All grades % (n)	Grade 3 % (n)
Fatigue	46.67% (21)	0
Hypertension	35.56% (16)	2.22% (1)
Thrombocytopenic	24.44% (11)	2.22% (1)
Loss of weight	22.22% (10)	0
Hand-foot skin reaction	20.00% (9)	0

AE evaluation was according to CTCAE v 5.0.

for more than 2 months were enrolled. The efficacy of LEN was evaluated by mRECIST criteria. AFP response was defined as 20% reduction from baseline. Child-pugh class was used to evaluate liver function. **Results:** A total of 45 patients were enrolled. 48.9% was TKI experienced and 51.1% was TKI naive, 8.9% was in Child-pugh B level. No patients showed complete response. 19.2%, 50% and 30.8% showed partial response and stable disease and progressive disease after one month and 50%, 25% and 25% after three months. The ORR of TKI naive and TKI experienced was 20% and 18.8% (1 mo) and 50% and 50% (3 mo) treatment. The AFP response rate was 58.3%. No patient was found who got a Child-pugh score above 7. The most common AEs were fatigue (46.67%), hypertension (35.56%) and thrombocytopenic (24.44%). The Grade 3 AE was only occurred in hypertension, and thrombocytopenic. **Conclusions:** This was the first real world data of LEN in Chinese HBV-related uHCC patients. LEN showed a similar response rate both in TKI naive and TKI experienced HBV-related HCC patients. The tolerability of LEN was acceptable even in child-pugh B patients. The difference of efficacy between the TKI naive and TKI experienced patients needs further study.

O-057

**Platelet-Albumin-Bilirubin Index:
A Valuable Assessment Method for
Prognostic Prediction in HCC Patients with
Child-Pugh Grade A Undergoing TACE
Combined Sorafenib**Keshu Hu^{1,2}, Jia Yuan^{1,2}, Bei Tang^{1,2}, Feng Zhang^{1,2},
Miao Li^{1,2}, Shenxin Lu^{1,2}, Rongxin Chen^{1,2},
Zhenggang Ren^{1,2}, Xin Yin^{1,2}¹Liver Cancer Institute & Zhongshan Hospital, Fudan University, China, ²Key Laboratory of Carcinogenesis and Cancer Invasion, Ministry of Education, China

Background and Aim: As combined therapy of TACE with Sorafenib has been frequently used in an increasing number of patients with intermediate-stage or advanced-stage HCC, the evaluation of pre-treatment liver function reserve becomes a major concern for the implementation of such aggressive treatment modality prone to induce severe liver function impairment and compromise patients' prognosis. We aim to validate the performance of two liver function assessment methods: ALBI and PALBI in the prediction of survival benefit in HCC patients with Child-Pugh grade A following TACE combined Sorafenib treatment. **Methods:** From 2004 to 2015, a total of 332 Child-Pugh grade A patients with BCLC stage B or stage C HCC undergoing TACE combined Sorafenib at Liver Cancer Institute, Zhongshan Hospital, Fudan University were retrospectively enrolled. Survival analyses were conducted and the discrimination efficacy were examined by C-index, area under receiver operator curve and Akaike information criteria. Subgroup analyses were also performed to investigate the potency of the two indexes in certain population of the patients. **Results:** When applying the two indexes to these Child-Pugh A HCC patients, two groups of survival by ALBI and three groups by PALBI were identified,

and the median overall survival was 13 vs. 8.5 months ($P < 0.05$) and 12 vs. 9 vs. 5 months ($P < 0.025$ both), respectively. PALBI was indicated to be associated with prognosis based on multivariate analyses ($HR = 1.61$, $P < 0.05$). Moreover, in comparison with ALBI, PALBI demonstrated better discrimination efficacy with a higher C-index and AUC, and a lower AIC. **Conclusion:** Both ALBI and PALBI can precisely evaluate pretreatment liver function reserve in these Child grade A patients. Notably, PALBI demonstrated more potent capacity of prognosis prediction than that of ALBI. Survival analysis indicates that patients with PALBI grade 1 are the best candidates for TACE plus Sorafenib therapy.

O-058

A Successful Treatment Case with Long-Term Survival for Hepatocellular Carcinoma Recurrence Post-Living Donor Liver Transplantation by Newly Molecular-Target TherapiesRyoichi Goto¹, Yoshikazu Ganchiku¹, Norio Kawamura¹, Masaaki Watanabe¹, Koji Ogawa², Toshiya Kamiyama¹, Tsuyoshi Shimamura³, Akinobu Taketomi¹¹Dept of Gastroenterological surgery I, Hokkaido University, Japan, ²Dept of Gastroenterology and Hepatology, Hokkaido University, Japan, ³Division of Organ transplantation, Hokkaido University Hospital, Japan

Background: Recent development of anti-angiogenic treatment for hepatocellular carcinoma (HCC) dramatically change the treatment strategies. We experienced a case with distant metastasis of HCC post-liver transplantation (LT) who achieved a long-term survival by combination treatment

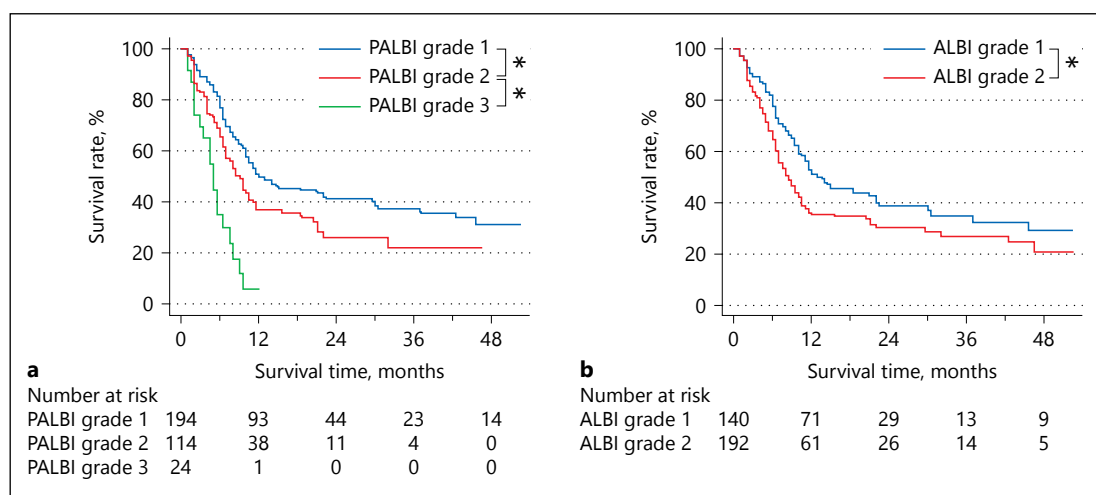


Fig. 1. (for Abstract no O-057).

including newly molecular-target therapies. **Case:** 62 years old man with HCCs beyond the Milan criteria which had developed in a HBV-liver cirrhosis, were transplanted a living liver gifting from his son. The lymph node metastasis was detected 2 months post-LT. The pleural dissemination of HCCs were diagnosed despite of TS-1 administration. The transient effectiveness of sorafenib was observed, however the continuous high dose of sorafenib was difficult by a severe hand-foot syndrome. Then surgical resection for dissemination of HCCs to the pleura was applied as much as possible, however remnant HCCs were immediately grown up again. At this timing the newly agent, regorafenib was approved as a second line for HCC in Japan. Regorafenib effectively reduced AFP level for 2 months, however, it was elevated again. Subsequently, lenvatinib was approved then its use dramatically induced tumor shrinkage and decreased AFP levels. However, the patient had a septic shock which discontinued a lenvatinib use for 3 months. No anti-cancer drug promoted HCC progression again. At the moment we applied lenvatinib again which gave long-SD. **Conclusion:** The patient had HCC metastasis immediate post-LT, however long-term survival with a better quality of life for more than 5 years post-transplantation has been achieved. Newly molecular-target drugs potentially provide a better outcome in HCC recurrence post-LT.

O-059

Post-Operative Lenvatinib for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Results from a Single Treatment Group

Haibin Zhang¹, Haibin Zhang¹

¹Eastern Hepatobiliary Surgery Hospital, China

Background: Previous studies showed the survival benefit of liver resection for hepatocellular carcinoma (HCC) associated with portal vein invasion [1], and adjuvant systemic therapy may prevent early recurrence in HCC patients with high risk factors [2]. However, the effect of post-operative lenvatinib for HCC with portal vein tumor thrombus (PVTT) has not been evaluated. **Methods:** Retrospective study was carried out on patients who underwent surgical resection for HCC complicated by PVTT (stage vp1 to vp4) in our single treatment group between 2016 and 2018. Patients with hepatic vein tumor invasion or lost to follow-up were excluded. Lenvatinib were administrated continuously for at least 4 months after hepatic resection. Time to recurrence and overall survival time were assessed. **Results:** A total of 34 patients were collected and eligible for final data analysis, of which 17 patients underwent post-operative lenvatinib. The median follow-up time was 9 months (range, 4–26). Median time to recurrence were 3 months (95% CI, 1 to 5) in lenvatinib group and 2 months (95% CI, 1 to 5) in control

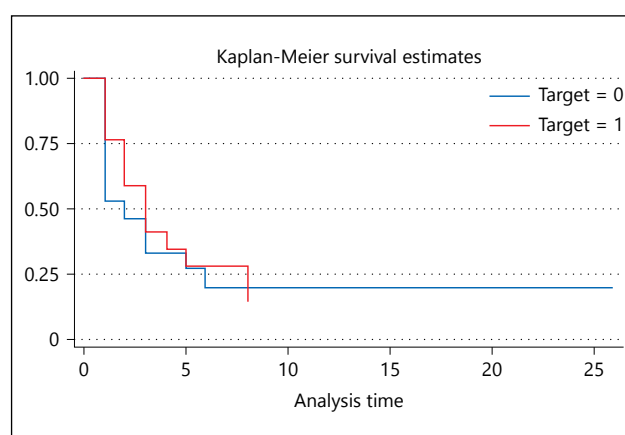


Fig. 1. Time to recurrence in lenvatinib group was 2 months, compared to 3 months in the control group (for Abstract no O-059).

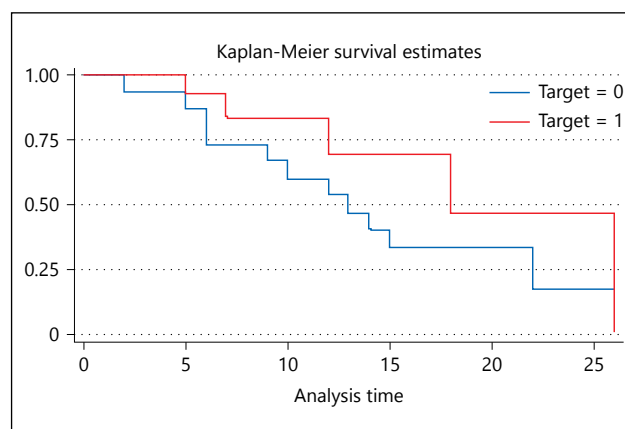


Fig. 2. The overall survival time in lenvatinib group was 18 months, compared to 18 months in the control group (for Abstract no O-059).

group (Fig. 1). The overall survival time in lenvatinib group was 18 months (95% CI, 7 to not reached), compared to 13 months (95% CI, 6 to 22) in the control group (Fig. 2). Hazard ratio for death was 0.64 (95% CI, 0.22 to 1.81; $P < 0.37$). **Conclusion:** Although not statistically significant, the survival benefit of post-operative lenvatinib can be inferred from the survival curve. The major drawback of this study is a short follow-up time (the median follow-up time is only 9 months). Prolonged follow-up was essential to draw a final conclusion.

O-060

Biomarkers of Treatment Response in Sorafenib and Lenvatinib for Patients with Unresectable HCCTaku Shigesawa¹, Goki Suda¹, Naoya Sakamoto¹¹Hokkaido University Graduate School of Medicine, Japan

Background: Lenvatinib and sorafenib are first-line systemic therapy for patients with unresectable-HCC. However, criterion for judgment which TKIs should be administered according to patients' condition is not clarified. We aimed to analyze serum cytokines which is related to treatment response in TKIs. **Methods:** We screened 80 and 35 patients with unresectable-HCC who were treated with sorafenib or lenvatinib between 2009 and 2018. Patients were included if they evaluated at baseline and 1–2 months after treatment initiation by dynamic-CT and had proper clinical information. Patients were excluded if treated with combination therapy of TKI and other therapy, no evaluation at proper point and insufficient clinical information. We evaluated treatment outcome by mRECIST and cytokines levels. **Result:** Of screened patients, 29 and 26 patients who were treated with sorafenib or lenvatinib and met inclusion criteria were included in this analysis. Mean age, sex, Child-Pugh classification were similar between two groups. Overall in the lenvatinib group, 3, 12, 7 and 4 patients were CR, PR, SD and PD respectively and, in the sorafenib group, 3, 19 and 7 patients were PR, SD and PD respectively. In lenvatinib, baseline ANG2 and FGF19 were significantly higher in SD+PD group (n = 11) compared with PR+CR group (n = 15). Additionally, in lenvatinib group, patients with CR had significantly lower pre-treatment ANG2 values compared with those in non-CR patients. In sorafenib also, ANG2 and FGF19 were higher in PD (n = 7) than PR+SD (n = 22) with a statistically significant difference. **Conclusion:** Baseline cytokine levels might predict treatment outcome in patients with unresectable HCC, who are treated with TKIs.

Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy

O-061

Predictors of Radiological Complete Response in Patients with Intrahepatic Hepatocellular Carcinoma Treated with Transarterial RadioembolizationYoon Ah Kim¹, Jae Seung Lee¹, Beom Kyung Kim^{1,2,3}, Jun Yong Park^{1,2,3}, Do Young Kim^{1,2,3}, Sang Hoon Ahn^{1,2,3}, Kwang-Hyub Han^{1,2,3}, Seung Up Kim^{1,2,3}¹Department of Internal Medicine, Yonsei University College of Medicine, Korea, ²Institute of Gastroenterology, Yonsei University College of Medicine, Korea, ³Yonsei Liver Center, Severance Hospital, Korea

Background/Aim: Transarterial radioembolization (TARE) has shown promising results for treating hepatocellular carcinoma (HCC). We identified the independent predictors of radiological complete response (rCR) in patients with intrahepatic HCC treated with TARE. **Methods:** Patients with intrahepatic HCC treated with TARE between 2011 and 2017 were recruited. The rCR was defined according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Cox-regression analysis was used to find independent predictors of rCR. **Results:** The median age of the study population (83 males and 19 females) was 64.3 years. The mean survival after TARE was 55.5 months and 21 (20.6%) patients were dead during the study period. The rCR was achieved in 14 (13.7%) patients who had significantly higher serum albumin level (median 4.1 vs. 3.9 g/dL), lower total bilirubin level (median 0.6 vs. 0.7 mg/dL), lower aspartate aminotransferase level (median 30.0 vs. 43.0 IU/L),

Table 1. Multivariate Cox-regression analysis to identify independent predictors of radiological complete response in patients with intrahepatic hepatocellular carcinoma treated with transarterial radioembolization (for Abstract no O-061)

Variables	Univariate		Multivariate analysis
	P value	P value	Hazard ratio (95% CI)
Serum albumin, g/dL	0.036	0.588	3.685 (0.033–415.239)
ALBI score	0.028	0.859	1.548 (0.013–189.867)
AST <32 IU/L	0.016	0.361	1.846 (0.495–6.889)
ALP <90 IU/L	0.042	0.573	1.526 (0.351–6.629)
MELD score	0.018	0.015	0.436 (0.224–0.849)
Maximal tumor size <9 cm	0.015	0.020	11.180 (1.458–85.731)

ALBI, Albumin-Bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; MELD, model for end-stage liver disease; CI, confidence interval.

lower alkaline phosphatase level (median 79.0 vs. 103.0 IU/L), lower alpha-fetoprotein level (median 12.7 vs. 39.9 ng/mL), lower des-gamma-carboxyprothrombin level (median 575.5 vs. 2772.0 mAU/mL), lower MELD score (median 6.0 vs. 7.0), and smaller maximal tumor diameter (median 6.3 vs. 9.0 cm) than those of patients without rCR (all $P < 0.005$). Multivariate Cox-regression analysis showed that lower MELD score (hazard ratio [HR]=0.436, $P = 0.015$) and maximal tumor size < 9 cm (HR = 11.180, $P = 0.020$) independently predicted the increased probability of radiological CR after TARE. **Conclusion:** Low MELD score and smaller maximal tumor size were independently associated with the increased probability of rCR after TARE in patients with intrahepatic HCC.

O-062

Curative Treatment after Transarterial Radioembolization Prolongs the Overall Survival of Patients with Hepatocellular Carcinoma

Yoon Ah Kim¹, Han Ah Lee², Jae Seung Lee¹,
Beom Kyung Kim^{1,3,4}, Jun Yong Park^{1,3,4},
Do Young Kim^{1,3,4}, Sang Hoon Ahn^{1,3,4},
Kwang-Hyub Han^{1,3,4}, Yeon Seok Seo², Seung Up Kim^{1,3,4}

¹Department of Internal Medicine, Yonsei University College of Medicine, Korea, ²Department of Internal Medicine, Korea University College of Medicine, Korea, ³Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea, ⁴Yonsei Liver Center, Severance Hospital, Seoul, Korea, Korea

Background/Aims: Transarterial radioembolization (TARE) has been used to treat hepatocellular carcinoma (HCC). We investigated whether curative treatment after TARE can prolong the overall survival in patients with HCC. **Methods:** A total of 102 patients with intrahepatic HCC treated with TARE between 2011 and 2017 were recruited. Subsequent curative treatment was applied according to the physician's decision. **Results:** The median age of the study population (83 males and 19 females) was 64.3 years. Twenty five (24.5%) patients received curative treatments (resection in 16, transplantation in 8, and ablation in 1) after TARE, who were likely to be younger (median 58.5 vs. 69.2 years) and less likely to have hypertension (9.8% vs. 48.0%) than those who did not receive curative treatments (all $P < 0.05$). On multivariate analysis, only younger age (< 65 years) was the only predictor of receiving curative treatment after TARE (hazard ratio [HR] = 5.681, 95% confidence interval [CI] 1.839–17.551, $P = 0.003$). In addition, non-curative treatment significantly predicted mortality ([HR] = 16.149, 95% [CI] 2.167–120.334, $P = 0.007$). On multivariate analysis, non-curative treatment was selected as an independent predictor of mortality (HR = 13.447, 95% CI 1.753–103.166, $P = 0.012$), together with multiple tumors (HR = 2.862), infiltrative tumor (HR = 3.119), maximum tumor

Table 1. Multivariate cox-regression analysis to identify the independent predictors of achieving curative treatment after TARE (for Abstract no O-062)

Variables	Hazard ratio (95% CI)	P value
Age < 65 years	6.210 (2.067–18.656)	0.001
Hypertension	0.515 (0.191–1.392)	0.191

TARE, trans-arterial radioembolization; CI, confidence interval.

diameter (HR = 1.140) and hepatic invasion (HR = 3.279) (all $P < 0.05$). The cumulative survival rate of patients who achieved curative treatment after TARE was significantly higher than that of patients who did not ($P < 0.001$ by log-rank test). **Conclusion:** Younger age independently predicted the increased probability of receiving curative treatment after TARE and curative treatment after TARE seems to provide a survival benefit in patients with intrahepatic HCC.

O-063

Irradiation Induces PD-L1 Upregulation by dsDNA Triggering cGAS-STING-IRF3 Pathway in Hepatocellular Carcinoma

Shisuo Du¹, Genwen Chen¹, QianQian Zhao¹,
Zhaochong Zeng¹

¹Zhongshan Hospital, Fudan University, China

Background/Aim: PD-L1 overexpression related to an aggressive phenotype in various cancer type. It has been reported that the irradiation (IR) upregulates PD-L1 and the mechanism remains unclear. Here we aimed to reveal the mechanism how irradiation affect PD-L1 expression in hepatocellular carcinoma (HCC). **Methods:** Irradiated HCC tissues and non-irradiated HCC tissues were performed with immunohistochemistry (IHC) to determined PD-L1 (SP142) expression. Real-time Quantitative PCR (qPCR), western blot, flow cytometry, immunofluorescence were used to detect the expression of PD-L1 and cGAS-STING signaling pathway in HCC cell lines. Chromatin immunoprecipitation (ChIP) and dual luciferase report assay were performed to validate the regulation of transcription factor IRF3 on PD-L1 promoter. **Results:** Clinical specimens showed a relative higher PD-L1 staining in irradiated than non-irradiated group. Also, higher PD-L1 expression correlated significantly with worse over survival (OS). PD-L1 increased in a dose-dependent manner both in mRNA and protein levels upon 0-2-4-8-12Gy irradiation in Huh7, HCCLM3 and MHCC97H cell lines in vitro. The cell surface PD-L1 level were confirmed substantially increased in a panel of HCC cells upon IR exposure. The Cancer Genome Atlas (TCGA) revealed a significant positive corre-

lation between cGAS-STING pathway activation and PD-L1 expression. cGAS-STING related gene expression was activated in a dose-dependent manner which is consistent with PD-L1 expression following IR. To further confirm that IR induced PD-L1 upregulation due to triggering cGAS-STING-IRF3 pathway, we knock down the key components of cGAS-STING pathway before IR. As expected, the upregulated PD-L1 expression upon IR was inhibited by silencing the cGAS, STING, TBK1 and IRF3 genes. ChIP-PCR and dual luciferase report assay verified that IRF3 directly targets PD-L1 promoter region and upregulates PD-L1 transcription after IR. Taken together, our findings demonstrated that cGAS-STING activation contributes to IR induced PD-L1 upregulation. **Conclusion:** Irradiation induced dsDNA triggering cGAS-STING-IRF3 pathway contributes to PD-L1 upregulation in HCC.

O-064

Carbon-Ion Radiotherapy for Intrahepatic Cholangiocarcinoma

Kei Shibuya¹, Akira Watanabe², Masahiko Okamoto^{1,3}, Shintaro Shiba³, Kenichiro Araki², Tatsuya Ohno¹, Ken Shirabe², Takashi Nakano^{1,3}

¹Gunma University Heavy-ion Medical Center, Japan,

²Departments of Hepatobiliary and Pancreatic Surgery and General Surgical Science Gunma University Graduate School of Medicine, Japan, ³Gunma University Hospital, Department of Radiation Oncology, Japan

Background/Aim: The prognosis of unresectable intrahepatic cholangiocarcinoma is extremely poor. We report on the treatment results of carbon-ion radiotherapy (C-ion RT) in intrahepatic cholangiocarcinoma not amenable to surgery. **Methods:** 16 patients who received C-ion RT between 2010 and 2018 (3 patients for Stage I, 10 for Stage II, 3 for stage IVA) were included in the study. Indications of C-ion RT were the following: (1) pathologically and clinically diagnosed intrahepatic cholangiocarcinoma, (2) unresectable cases without intrahepatic metastasis or distant metastasis, and (3) direct invasion to gastrointestinal tract direct, (4) ECOG-performance status (PS) ≤ 2 , (5) Child-Pugh Class A or B. The prescribed dose is 52.8 Gy (RBE) or 60.0Gy (RBE) in 4 or 12 fractions. **Results:** Local recurrence was observed in 3 patients. Local control rates at both 1 and 2 years were 80.8%. five patients experienced intrahepatic recurrence at other sites, and extrahepatic metastasis occurred in nine cases (5 patients for lung metastasis, 4 for lymph node metastasis, and 1 for peritoneal dissemination). Progression free survival at 1 and 2 year were 29.5% and 14.7%, respectively. Eight patients died of primary disease. Overall survival at 1 and 2 years were 69.6% and 40.6%, respectively. Grade 2 or greater acute toxicities were not observed. Two patients experienced grade 3 toxicities in late phase: liver abscess required percutaneous drainage, and

obstructive jaundice due to bile duct stenosis required biliary drainage. **Conclusions:** C-ion RT may be an effective treatment option for inoperable intrahepatic cholangiocarcinoma.

Treatment: Systemic, Targeted, Novel Target or Experimental Therapy

O-065

Apatinib Combined with Radiotherapy for Unresectable Hepatic Carcinoma

Yongshun Chen¹, Shaobo Ke¹, Hu Qiu¹, Jiamei Chen¹, Wei Shi¹, Yi Gao¹, Yi Gong¹, Jing Wang¹, Chen Han¹

¹Renmin Hospital of Wuhan University, China

Background: Hepatic carcinoma is characterized with high heterogeneity and advanced disease is a lethal cancer, a significant proportion of patients with advanced disease are left with limited therapeutic options and poor survival. This prospective study (ChiCTR-OPC-17011890) was designed to determine the clinical outcomes and safety of Apatinib with radiotherapy for patients with advanced hepatic carcinoma. **Methods:** Major eligibility criteria include historically confirmed unresectable hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma patients with Child-Pugh Class A or B liver function, ECOG PS 0 or 1. Radiotherapy was given either concurrently (1 day after the first dose) or sequentially (1 month after the first dose) with Apatinib (500 mg, QD), and restaging imaging was performed every 8 weeks until progression. The primary endpoint was progression free survival (PFS). Secondary endpoints included overall response rate (ORR), overall survival (OS) and treatment related adverse events (TRAEs). **Results:** As of August 1, 2018, 26 of a planned 49 patients were enrolled. The cohort had a median age of 59 years (range 32–77), ECOG PS 0/1 (10/16), male/female (22/4). 23 patients had hepatitis (88%), 18 had Child Pugh A (69%). 24 were diagnosed with HCC, and 7 had portal vein involvement (27%). 15 patients had received concurrent treatment and 11 received sequential treatment. There were 6 (23%) grade 3 TRAEs including neutropenia, thrombocytopenia, hypertension, proteinuria and hand and foot syndrome. No grade 4 TRAEs were observed, and no patients were taken off study due to TRAEs. Two patient (7.7%) achieved complete response, 8 (30.8%) achieved partial response, and 14 (53.8%) had stable disease, 2 (7.7%) had progressive disease, respectively. **Conclusions:** Apatinib combined with radiotherapy was well tolerated with encouraging anti-tumor activity in patients with advanced hepatic carcinoma.

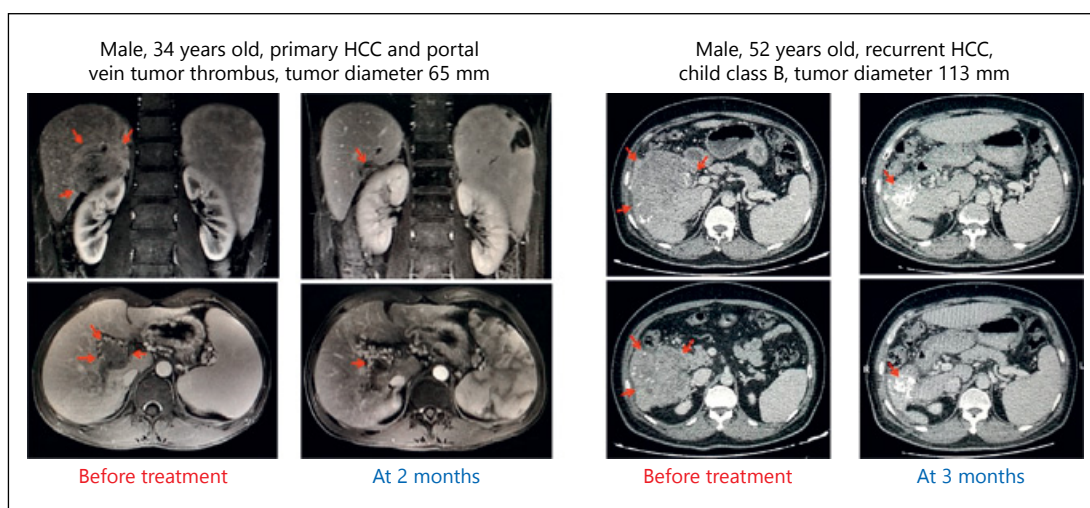


Fig. 1. (for Abstract no O-065).

O-066

Anti-PD-1 With or Without Sorafenib for Advanced Hepatocellular Carcinoma – A Single Institute Experience

San-Chi Chen¹, Yi-Hsiang Huang¹, Ming-Huang Chen¹, Yi-Ping Hung¹, Hao-Jan Lei¹, Gar-Yang Chau¹, Chien-An Liu¹, Rheun-Chuan Lee¹, Yee Chao¹

¹Taipei Veterans General Hospital, Taiwan

Background/Aim: Sorafenib and anti-PD-1 are potent drugs for hepatocellular carcinoma (HCC). This study aims to investigate the efficacy of anti-PD-1 with or without low-dose sorafenib in HCC. **Methods:** We retrospectively analyzed HCC patients who received anti-PD-1 therapy in our institute. Results Among 156 HCC patients, 70 patients had combination therapy and 86 had anti-PD-1 alone. Nivolumab was used in 130 patients and pembrolizumab in 26 patients. The combination group had more Child-Pugh Score (CPS) C (18.6% vs. 1.2%, $p < 0.05$), portal vein thrombosis (74.3% vs. 46.5%, $p < 0.05$) and BCLC stage D (21.4% vs. 1.2%, $p < 0.05$) than anti-PD-1 group, but similar sorafenib experienced (54.3% vs. 58.1%). The combination group had higher disease control rate (CR: 11.5%, PR: 13.5%, SD: 42.3% vs. CR:5.1%, PR:15.2%, SD:13.9%, $p < 0.05$) and longer PFS (4.2 vs. 2.4 months, $p < 0.05$). Patient characteristics including etiology, CPS, metastasis, AFP level were not associated with treatment response. The OS of combination group was not superior to anti-PD-1 group owing to worsen liver function. In general, responders had significantly prolonged survival comparing with non-responders (28.9 vs. 11.1 months, $p < 0.05$), regardless of CPS A (32.3 vs. 14.4 months) and CPS B/C (16.6 vs. 3.7 months). Multi-variant analysis showed that combination of sorafenib (HR: 0.51, $p < 0.05$) was a protective factor for progression and CPS B/C (HR:3.09, $p < 0.05$), AFP level >20 ng/mL

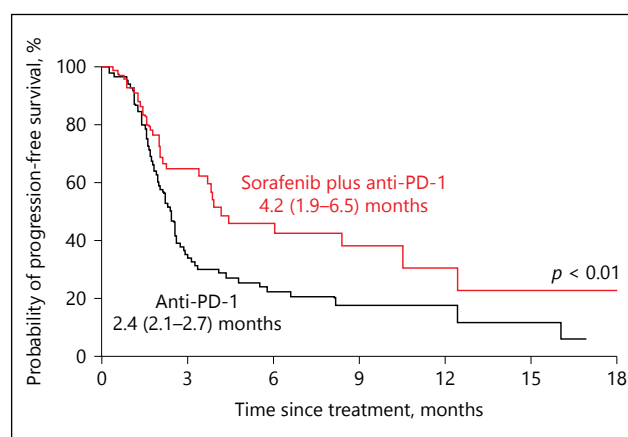


Fig. 1. (for Abstract no O-066).

(HR:2.14, $p < 0.05$) were risk factors for survival. **Conclusions:** This study demonstrated higher response rate and longer PFS with the combination therapy. Responders significantly prolonged survival regardless of their liver function. This study would serve as an important reference for the combination therapy in the future.

O-067

Regorafenib versus Nivolumab for Hepatocellular Carcinoma Patients Who Experienced Sorafenib Treatment Failure: A Propensity Score Analysis

Cheol-Hyung Lee¹, Yun Bin Lee¹, Minseok Albert Kim¹, Heejuon Jang¹, Sun Woong Kim¹, Eun Ju Cho¹, Kyung-Hun Lee^{2,3}, Jeong-Hoon Lee¹, Su Jong Yu¹, Jung-Hwan Yoon¹, Tae-You Kim^{2,3}, Yoon Jun Kim¹

¹Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, Korea, ²Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, Korea, ³Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea, Korea

Aims: Several treatment options are now available for patients with hepatocellular carcinoma (HCC) who progress during sorafenib treatment. We aimed to compare the efficacy of regorafenib and nivolumab in HCC patients who have failed sorafenib treatment. **Methods:** Consecutive patients who received regorafenib or nivolumab for the treatment of HCC after sorafenib treatment failure between July 2015 and October 2018 at Seoul National University Hospital were included in this retrospective study. Primary endpoint was overall survival. Inverse probability weighting (IPW) using propensity scores was conducted to reduce the treatment selection bias. **Results:** Among 151 included HCC patients, 103 patients received regorafenib and 48 patients received nivolumab. During the median (interquartile range) follow-up of 4.1 (2.8–6.2) months, 66 of 151 patients (43.7%) died: 39 of 103 patients (37.9%) receiving regorafenib and 27 of 48 patients (56.3%) receiving nivolumab. Median survival was

6.4 months (95% confidence interval [CI], 2.4–10.4) for regorafenib and 5.9 months (95% CI, 3.7–8.1) for nivolumab ($P = 0.82$ by log-rank test) (Fig. 1A). Overall survival was not significantly different between the groups (nivolumab vs. regorafenib: adjusted hazard ratio [aHR], 0.81; 95% CI, 0.48–1.36; $P = 0.42$). Even after balancing baseline characteristics using IPW, overall survival was still similar between the groups ($P = 0.21$ by log-rank test) (Fig. 1B). However, patients treated with nivolumab showed significantly prolonged overall survival compared to patients treated with regorafenib (aHR, 0.48; 95% CI, 0.25–0.91; $P = 0.03$) after adjusting for baseline characteristics including the levels of alkaline phosphatase, aspartate aminotransferase, and MoRAL score ($=11 \times \text{sqrt (PIVKA)} + 2 \times \text{sqrt (AFP)}$), Child-Pugh class, and the presence of clinically significant portal hypertension. **Conclusions:** Improved overall survival was demonstrated in patients who were treated with nivolumab compared to patients who were treated with regorafenib after rigorous adjustment for baseline demographic and clinical characteristics.

O-068

The Integration of Radiotherapy with Anti PD-(L)1 Immunotherapy for the Treatment of Intrahepatic Cholangiocarcinoma

Qianqian Zhao¹, Zhaochong Zeng¹

¹Zhongshan Hospital, Fudan University, China

Background: Intrahepatic cholangiocarcinoma (ICC) represents a clinically challenging disease with a dismal prognosis. A therapeutic plateau had been reached with the traditional treatments. However, with immunotherapy advances in

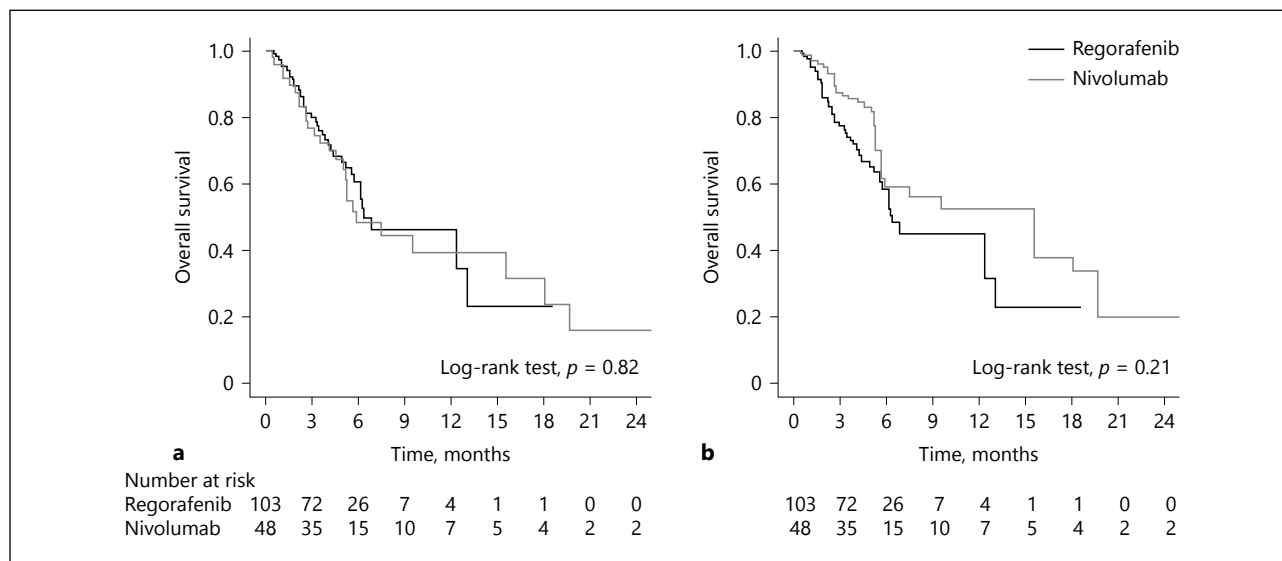


Fig. 1. (for Abstract no O-067).

cancer therapy, integration of stereotactic body radiotherapy (SBRT) with anti PD-1 or PD-L1 immunotherapy has been demonstrated a synergistic effect and high clinical efficacy in many cancer types. This combination may shed light on potential breakthrough in the treatment of this fatal malignancy. **Methods:** In this paper, we reported four cases with refractory advanced ICC were successfully controlled with anti PD-1 immunotherapy following SBRT. **Results:** The devastating cancer of all cases was successfully controlled with anti PD-1 immunotherapy following SBRT. The median overall survival of them was longer than 1 year, much longer than that of the advanced ICC treated with the other traditional treatments. Among them, one case showed that the unique response pattern of pseudoprogression during the course treatment with Nivolumab. One case indicated that different immunotherapy drugs may have different response, even they are all anti PD-1 antibody. What's more, there is one case of initially unresectable got the chance of an operation after this novel combined therapy. We further explored challenges of developing predictive biomarkers of anti PD-1 immunotherapy responsiveness based on our cases data. We also discussed the regulation effect of SBRT on tumor micro-environment and the potential advantages of this combination regime for this aggressive disease, which would be important considerations and provide some directions for future clinical trial designs. **Conclusion:** Our cases showed that the integration of SBRT with anti-PD-1 immunotherapy possibly has a synergistic effect on ICC, and this kind of combination was tolerated well with no severe adverse events observed during the therapy. This regimen might provide a new therapeutic option and represent a promising potential treatment pattern for ICC.

O-069

Hepatitis B Virus Reactivation and Flare in Patients with Advanced Hepatocellular Carcinoma Receiving Immune Checkpoint Inhibitors: A Single Centre Experience

Joycelyn JX Lee¹, Andrea Ang¹, Lawrence Wong¹, Kennedy Ng¹, David WM Tai¹, Su Pin Choo¹

¹Division of Medical Oncology, National Cancer Centre Singapore, Singapore

Hepatitis B virus (HBV) is a common etiology of hepatocellular carcinoma (HCC) in Asia. Patients with HBV enrolled into CheckMate-040 and Keynote-224 were required to be on anti-viral treatment and have HBV DNA viral load (VL) <100 IU/mL. We describe our centre's real world experience with immune checkpoint inhibitors (ICI) in patients with advanced HBV-related HCC. We retrospectively identified 62 patients with HBV-related HCC who received ICI between May 2015 - Nov 2018. We described the incidence of HBV reactivation, flare and hepatic adverse events (AE). HBV reactivation was defined as an increase in VL >10x baseline, appearance of previously undetectable DNA titres, or new HBsAg reactivity. HBV flare was defined as HBV reactivation with a rise in ALT >5x ULN. Hepatic AE referred to any elevation in ALT, AST, ALP, or bilirubin according to CTCAE v4.03 grading. 53 (85.5%) patients were males, median age was 60.3 years, 61 (98.4%) had ECOG PS 0/1 and 49 (79.1%) were Child-Pugh A5-6. 38 (61.3%) received ICI as monotherapy. 55 (88.7%) had baseline VL measured, with a median of 40 IU/mL (0–8210000 IU/mL). 57 (91.9%) were on anti-virals. 16 (25.8%) had hepatic AE, 4 were grade 3/4. Amongst patients on anti-virals, 5 (8.8%) developed HBV reactivation. None had flares or required treatment discontinuation. Of the 5 patients not on anti-virals, one had HBV reactivation and flare requiring treatment discontinuation. Patients on anti-virals had fewer grade 3/4 hepatic AEs than those without (3.5% vs 40.0%, p = 0.001). VL >100 IU/mL was not associated with increased risk of HBV reactivation or flare. All patients with HBV-related HCC planned for ICI should be on anti-virals. ICI use in patients with high baseline VL may still be safe provided that anti-virals are concurrently administered.

Poster Session

Biomarkers / Cell Biology and
Translational Research

P-001

MicroRNA-148a-5p Inhibits CD44 Expression
and Epithelial-Mesenchymal Transitions in
Hepatocellular Carcinoma Cells*Si Hyun Bae^{1,2}, Na Ri Park², Jung Hoon Cha²,
Sung Woo Cho², Jeong Won Jang^{1,2}, Jong Young Choi^{1,2},
Seung Kew Yoon^{1,2}*¹Department of Internal Medicine, College of Medicine,
The Catholic University of Korea, Seoul, Korea, Korea,²The Catholic University Liver Research Center, College
of Medicine, The Catholic University of Korea, Seoul,
Korea, Korea

Background/Aims: CD44 have known as important modulators of epithelial-mesenchymal transition (EMT) together with transforming growth factor beta1 (TGF- β 1). Moreover, CD44 and TGF- β 1 double positive more enhanced cancer stem cell characteristics acquisition, EMT, and metastasis. This study aimed to investigate the role of miR-148a-5p regulating the EMT as well as CD44/TGF- β 1 expression in HCC. **Methods:** We sorted CD44⁻ and CD44⁺ liver cancer stem cells by fluorescence-activated cell sorting (FACS) in TGF- β 1-positive SNU-368 cells and TGF- β 1-negative SNU-354 cells. The miRNAs expression profiles of CD44 sorted cells and TGF- β 1-treated SNU-354 cells were analyzed through next-generation sequencing (NGS). miR-148a-5p mimic and inhibitors were transfected into HCC cells. The expression of mRNA and protein were detected by quantitative real-time PCR (qRT-PCR) and western blot. **Results:** FACS analysis showed high expression of CD44 in two HCC cell lines with different levels of TGF- β 1 expression. SNU-354 CD44⁺ cells with no TGF- β 1 expression only showed increased N-cadherin expression, with no significant changes in E-cadherin expression. However, TGF- β 1-stimulated SNU-354 cells (CD44⁺/TGF- β 1⁺) and SNU-368 CD44⁺ cells exhibited lower E-cadherin and higher N-cadherin. We identified different miRNAs between two groups (SNU-354 CD44⁻ vs CD44⁺ cells and SNU-354 con vs TGF- β 1-treated cells), among which miR-148a-5p expression level was up-regulated in SNU-354 CD44⁺ cells and was down-regulated in SNU-354 TGF- β 1-stimulated cells. Simi-

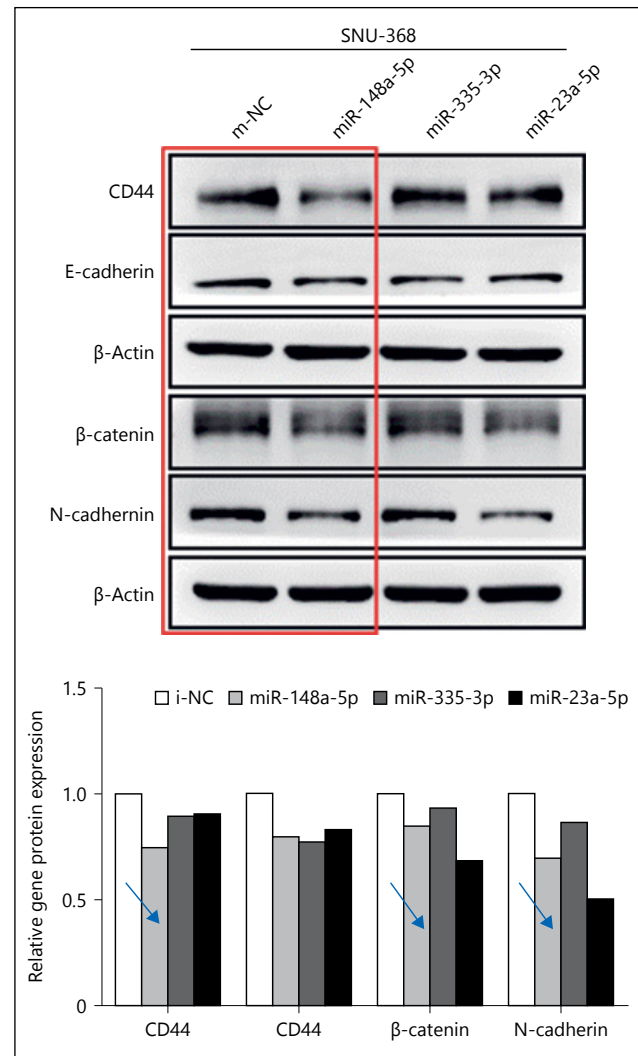


Fig. 1. (for Abstract no P-001).

larly, miR-148a-5p expression was also down-regulated in SNU-368 CD44⁺ cells. The Inhibition of miR-148a-5p in SNU-354 (CD44⁺/TGF- β 1⁻) cells induced EMT and cell migration. In contrast, overexpression of miR-148a-5p in SNU-368 (CD44⁺/TGF- β 1⁺) cells reduced mesenchymal marker and cell migration as well as down-regulation of CD44. Also, TGF- β 1 stimulation after miR-148a-5p overexpression induced neither the mesenchymal phenotype nor cell migration in SNU-354 cells. **Conclusions:** We identified CD44/TGF- β 1-related miRNAs and among them, miR-

148a-5p have been confirmed to regulate EMT. The results suggest that CD44/TGF- β 1-associated miR-148a-5p may serve as specific biomarkers and therapeutic targets for HCC.

P-002

Metformin Contributes to Collagen Type 1 Production in Liver Cancer of T2-Diabetic Rat

Wahyuni Lukita Atmodjo^{1,2}, Young Larasati Othiwi², Riska Nufika², Erni Sulistiawati³, Imelda Winoto², Irawan Yusuf²

¹Universitas Pelita Harapan-MRIN, Indonesia, ²Mochtar Riady Institute of Nanotechnology, Indonesia, ³Bogor Institute of Agriculture, Indonesia

Background: The complications of diabetes, including liver fibrosis towards liver cancer is experienced by a majority of type 2 diabetic. Metformin as anti-hyperglycemic agent have been shown to activate protein kinase, AMPK, that act against hepatic fibrogenesis in the process of liver carcinogenesis. The aim of this study is to explore the contribution of metformin to the production of collagen type 1 in liver fibrosis of T2 diabetic rat. **Material and Methods:** Twenty four male T2 diabetic Wistar rats at seven weeks of age, divided into 3 groups as follows, group 1 is T2D rats (n = 9) as negative control; group 2 is T2D rats injected with Diehynitrosamine (DEN) (n = 9) as positive control; and group 3 is T2D rats injected with DEN and given metformin 250 mg/kg BW in drinking water (n = 6) as metformin group. All groups of rat were sacrificed at week 10 after first injection of DEN. The liver tissue were collected and stored in both RNAlater and Buffer Neutral Saline for measuring the proteins level of p-AMPK and Collagen type 1. The fixated liver were prepared for histology specimens and stained for Hematoxylin and Eosin. The serum were taken every week to test their fasting blood glucose. **Result:** Liver sections showed development of tumor nodules consists of pre-neoplastic cells with abundant

prominent nucleoli. Liver fibrosis grade mild to severe were seen to form pseudo nodules. In the group of rats treated with metformin demonstrated increasing level of p-AMPK protein and decreasing the level of collagen type 1 compare to positive control group of rats injected with DEN. The level of Fasting Blood Glucose taken every week showed decreasing level significantly. **Conclusion:** This study suggested that increasing level of p-AMPK after administration of metformin may suppressed the production of collagen type 1 in liver fibrosis.

P-003

Relationship Between Change in α -Fetoprotein (AFP) and Patient Survival in Hepatocellular Carcinoma (HCC): A Real-World Electronic Medical Records Database Study

Yoshinori Tanizawa¹, Lisa M. Hess², Zhanglin L. Cui², Tomoko Sugihara³, Yun Fang³, Allicia C. Girvan², Paolo B. Abada²

¹Eli Lilly Japan, Japan, ²Eli Lilly and Company, USA,

³Syneos Health, USA

Background: Serum AFP levels are used as a diagnostic and prognostic marker for patients (pts) with HCC. Assessment of the clinical relevance of changes in AFP over time outside of clinical trials is lacking. This study was designed to explore the relationship between changes in AFP levels and overall survival (OS) in a real-world setting. **Methods:** This retrospective analysis used the IMS Oncology electronic medical record (EMR) database (US patients, 12/01/2007–12/31/2014). Eligible pts were diagnosed with HCC, 18+ years old, had at ≥ 1 AFP test recorded 60 days prior to 180 days after diagnosis, and received anticancer therapy ≤ 180 days after diagnosis. Survival analyses were by Kaplan-Meier method. The gamma-frailty model was used to correlate AFP change utilizing previously-reported definitions of AFP change (above/below 400 ng/mL, ≥ 20 ng/mL, ≥ 7 ng/mL/month, $\pm 20\%$, $\pm 50\%$) and OS. **Results:** A total of 907 pts met

Table 1. Relationship between change in AFP and OS (for Abstract no P-003)

Observed AFP change during 1L	N	Median OS (95% CI), months	Cross ratio	Kendalls Tau
Decrease ($\downarrow$) to <400 from ≥ 400 ng/mL	20	14.3 (4.8–30.9)	1	0
$\downarrow \geq 20$ ng/mL	85	7.4 (5.7–11.9)	1	0
$\downarrow \geq 7$ ng/mLmonth	68	6.8 (5.0–12.7)	1	0
$\downarrow \geq 20\%$	98	11.1 (7.3–13.2)	1	0
$\downarrow \geq 50\%$	51	12.2 (7.3–18.2)	1	0
Increase ($\uparrow$) to ≥ 400 from <400 ng/mL	18	5.9 (3.6–7.4)	1.506	0.202
$\uparrow \geq 20$ ng/mL	140	4.8 (3.7–5.5)	1.902	0.311
$\uparrow \geq 7$ ng/mLmonth	124	4.5 (3.1–5.2)	2.006	0.335
$\uparrow \geq 20\%$	141	5.2 (4.1–6.5)	1.841	0.296
$\uparrow \geq 50\%$	109	5.4 (4.5–6.9)	1.755	0.274

eligibility criteria (77.3% male, median 65 years of age). Of 697 pts with AFP prior to start of first-line therapy, the 453 (65%) with a baseline AFP less than 400 ng/mL had an OS of 4.2 months and the 244 (35%) with ≥ 400 ng/mL an OS of 2.9 months. An increase in AFP was associated with a decrease in OS in the 278 patients with baseline and first-line therapy (1L) AFP (Table). Of the 101 pts with an AFP test before start of second line therapy, 32.7% had AFP ≥ 400 ng/mL. **Conclusions:** Increases and decreases in AFP during 1L, regardless of AFP change definition, were generally associated with shorter and longer OS, respectively. Conclusions are limited by the risk of immortal time and selection bias, as not all patients had multiple AFP measures recorded. This poster was previously presented at ESMO 2018.

P-004

Exosome Derived Circular Non-Coding RNA Panel as Biomarkers for Early Diagnosis of Hepatocellular Patient

Jung Woo Eun¹, Geum O.K. Baek¹, Chul Won Seo¹, Hye R.I. Ahn¹, Hyo Jung Cho¹, Soon Sun Kim¹, Jae Youn Cheong¹

¹Department of Gastroenterology, Ajou University School of Medicine, Suwon, Korea

Background: Currently, none of the available hepatocellular carcinoma testing has been established as a well assessed diagnosis tool, particularly for the early stage of hepatocellular carcinoma. The recent discovery of exosome noncoding RNAs, microRNA and long non-coding RNA, profile has provided a novel approach for tumor diagnosis. We aimed to investigate specific exosome noncoding RNAs underlying early progression of HCC that can be detected in precancerous lesions. **Methods:** We designed noncoding RNAs selection strategy to identify potential drivers by integrative analysis of noncoding RNome and clinicopathological data of human multistage HCC tissues, including noraml liver, chronic hepatitis, liver cirrhosis, early HCC, and advanced HCC. Using various computational approaches, we selected miRNA candidates and, differentially expressed serum non-coding RNAs were tested by the reverse transcription PCR in the test cohort. The non-coding RNA panel was developed with a logistic regression model and validated using an independent cohort. Receiver operating characteristic curves were constructed to evaluate the diagnostic accuracy of the panel. **Results:** The a combined analysis of clinicopathological data and miRNA expression data revealed six miRNAs significantly higher eHCC than non-tumors. After the selection and validation process via reverse transcription PCR, we identified a four miRNAs and three lncRNAs panel with a high diagnostic accuracy of eHCC.

P-005

Molecular Characteristics Associated with 18F-FDG Uptake in Intrahepatic Cholangiocarcinoma

Koo Jeong Kang¹, Keun Soo Ahn¹, Yong Hoon Kim¹, Tae-Seok Kim¹, Kyoung Sook Won¹

¹Keimyung University Dong San Hospital, Korea

Background: In intrahepatic cholangiocarcinoma (iCCA), genetic characteristics on 18F-FDG-PET scans are not yet clarified. If they are evaluated, we can predict molecular features based on the FDG uptake. We analyzed RNA sequencing in iCCA patients to evaluate gene expression signatures associated with FDG uptake patterns. **Methods:** We performed RNA sequencing of 22 cases iCCA who underwent preoperative 18F-FDG- PET, and analyzed the clinical and molecular features according to the maximum standard uptake value (SUVmax). Genes and biological pathway which are associated with SUVmax were analyzed. Results Patients with SUVmax higher than 9.0 (n = 9) had poorer disease-free survival than those with lower SUVmax (n = 13, P = 0.035). Genes related to glycolysis and gluconeogenesis, phosphorylation and cell cycle were significantly correlated with SUVmax ($r \geq 0.5$ or $r \leq -0.5$). RRM2, which is related to the toxicity of Gemcitabine was positively correlated with SUVmax, and SLC27A2 which is associated with Cisplatin response was negatively correlated with SUVmax. Cell cycle, hypoxia and metabolism-related pathways were enriched in high SUVmax patients. Conclusion The genomic features of gene expression and pathways can be predicted by FDG uptake features in iCCA. Patients with high FDG uptake have enriched cell cycle, metabolism and hypoxic pathways, which may lead to a more rational targeted treatment approach.

P-006

Tumor-Stroma Crosstalk Enhances REG3A Expressions That Drive the Progression of Hepatocellular Carcinoma

Yuri Cho¹, Min Ji Park¹, Koeun Kim¹, Jung-Hwan Yoon²

¹Department of Internal Medicine, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Republic of Korea, Korea, ²Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, Korea

Background: Crosstalk between tumor and their micro-environment plays a crucial role in the progression of hepatocellular carcinoma (HCC). However, there is little existing information about the key signaling molecule that modulates tumor-stroma crosstalk. **Methods:** Complementary DNA (cDNA) microarray analysis was performed to identify the key

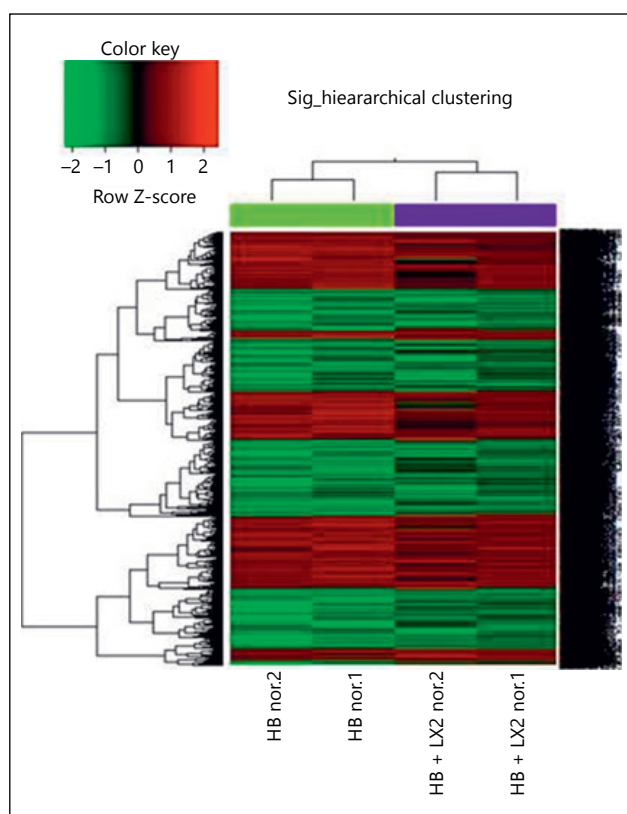


Fig. 1. (for Abstract no P-006).

molecule in tumor-stroma crosstalk. Subcutaneous xenograft in vivo murine model, immunoblotting, immunofluorescence, and real-time polymerase chain reaction using HCC cells and tissues were performed. **Results:** The novel molecule, regenerating gene protein-3A (REG3A), was most significantly enhanced when coculturing HCC cells and activated human hepatic stellate cells (HSCs) (+ 8.2 log) compared with monoculturing HCC cells using cDNA microarray analysis. Down-regulation of REG3A using small interfering RNA significantly decreased the proliferation of HSC-cocultured HCC cells in vitro and in vivo, and enhanced deoxycholic acid-induced HCC cell apoptosis. Crosstalk-induced REG3A upregulation was modulated by platelet-derived growth factor $\beta\beta$ (PDGF- $\beta\beta$) in p42/44-dependent manner. REG3A mRNA levels in human HCC tissues were upregulated 1.8-fold compared with non-tumor tissues and positively correlated with PDGF- $\beta\beta$ levels. **Conclusions:** REG3A/p42/44 pathway/PDGF- $\beta\beta$ signaling plays a significant role in hepatocarcinogenesis via tumor-stroma crosstalk. Targeting REG3A is a potential novel therapeutic target for the management of HCCs by inhibiting crosstalk between HCC cells and HSCs.

Viral Hepatitis / Cirrhosis and Related Complications

P-007

Hepatocellular Carcinoma in Patients with Non-Cirrhotic Liver at Mandalay General Hospital, Myanmar

Moe Z. Maung¹, Kyaw T. Tun¹, Sithu Lin¹, Khin T. Myint¹, Thandar Tun¹, Naomi K.T. Hlaing¹

¹University of Medicine, Mandalay, Myanmar

Background: Hepatocellular carcinoma (HCC) typically arises in cirrhotic liver. However, it is stated that approximately 20% of HCC occur in non-cirrhotic liver (NCL) and these cases present at the advanced stage of the disease [1]. **Aim:** To study the demographic data, aetiology and staging of HCC in NCL at the Mandalay General Hospital (MGH), Myanmar. **Methods:** Total 82 patients with HCC admitted to Department of Hepatology, MGH from September to November, 2018 were consecutively studied. **Results:** The number of patients with HCC in NCL was 27 out of 82 (33.3%). Fifty percent (12/24) of HBV, 30% (12/40) of HCV, 16.6% (1/6) of HBV-HCV co-infection and 16% (2/12) of alcoholic liver diseases had HCC in NCL. The mean age of patients with HCC in NCL was 48.2 years. The mean age of patients with HBV induced and HCV induced HCC in NCL were 43.3 years and 61.8 years respectively. HBV related HCC in NCL was more common in male (7/12) and HCV related was more common in female (8/12). Regarding with the staging, 16.6% (2/12) of HBV

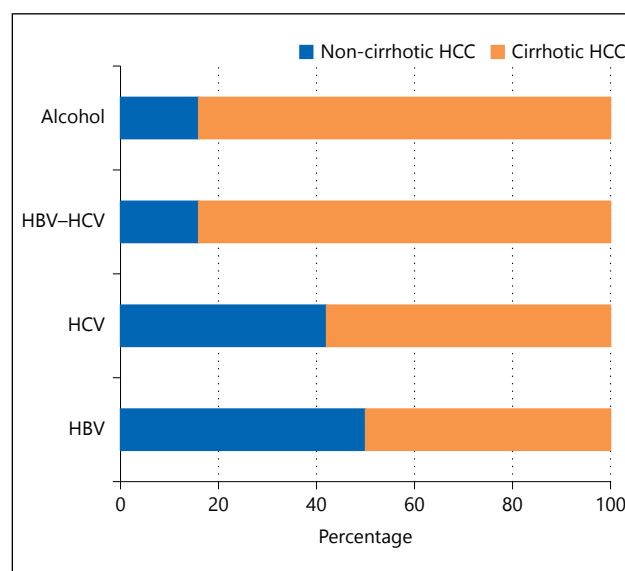


Fig. 1. Prevalence of non-cirrhotic HCC according to aetiology (for Abstract no P-007).

related cases and 41.7% (5/12) of HCV related cases presented

Conclusion: Non-cirrhotic HCC was more common in HBV than HCV infection and alcoholic liver diseases. HBV induced HCC patients in NCL were younger than those with HCV. However, advanced stage at presentation was more common in HCV than HBV related HCC in NCL. Regardless of aetiology, about one third of HCC did not have associated cirrhotic features. Therefore, patients with chronic liver diseases should be in regular HCC surveillance program with or without associated cirrhosis.

References

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P-008

Stage of Hepatocellular Carcinoma at the Time of Diagnosis in Mandalay General Hospital, Myanmar

Sithu Lin¹, Khin T. Myint¹, Moe Z. Maung¹, Kyaw T. Tun¹,
Nang K.T. Win¹, Naomi K.T. Hlaing¹

¹University of Medicine, Mandalay, Myanmar

Background: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death worldwide. It is a heterogeneous disease and treatment varies according to the liver function, portal hypertension, physical performance status and tumor burden. Barcelona Clinic Liver Cancer (BCLC) staging is currently used in management of HCC. Treatment allocation and patients survival vary with the BCLC stages.

Aim: To study the BCLC staging of the patients with HCC at the time of diagnosis which can influence the treatment allocation and patient survival.

Method: The study involved 70

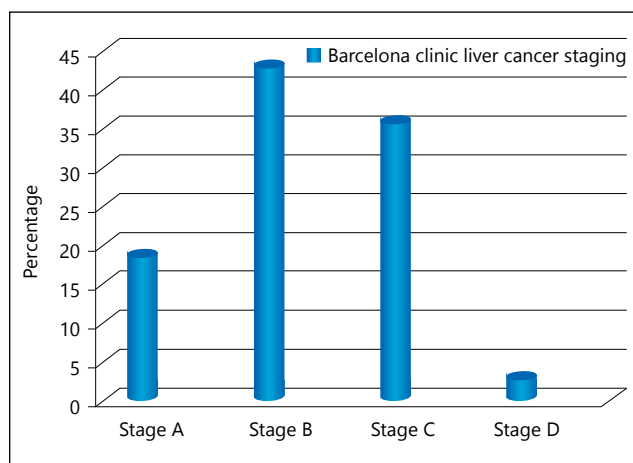


Fig. 1. Staging of HCC according to Barcelona Clinic Liver Cancer staging (for Abstract no P-008).

patients with HCC at the Department of Hepatology, Mandalay General Hospital from December 2018 to April 2019. HCC was diagnosed by arterial phase hyperenhancement and washout on portal venous and or delayed phases in contrast enhanced CT scan liver. Child Pugh Grades, performance status, tumor size and numbers, vascular involvement and distant metastasis were studied.

Results: Male HCC was more than female. Mean age was 53.43. The aetiologies of the patients with HCC were viral hepatitis B (54.3 %), viral hepatitis C (35.7%), viral hepatitis B and C coinfection (2.8%), patients without viral hepatitis B and C (7.2%). All the patients had cirrhosis. Most (81.4%) of the patients were in advanced stage at the time of diagnosis, with 42.9% in stage B, 35.7% stage C and 2.8% stage D. Early HCC (Stage A) was seen in only 18.6%.

Conclusion: This study showed the extent of late stage of HCC in my center. Although it is a small study, it may reflect the real situation of HCC and the necessity of implementation of vigilant HCC surveillance program in Myanmar for timely intervention and effective treatment.

P-009

The Risk of Hepatocellular Carcinoma in Cirrhosis Combined with OGTT Confirmed Diabetes

Moon Young Kim¹, Seong Hee Kang¹, Soon Koo Baik¹,
Sung Hee Woo¹

¹Yonsei University Wonju College of Medicine, Korea

Background and Aims: We aim to identify potential predictors of HCC, who were newly-diagnosed as having DM by oral glucose tolerance test (OGTT).

Methods: This prospective observational study included 713 patients with either compensated or decompensated cirrhosis; these patients underwent a 75 g oral glucose tolerance test (OGTT).

Results: Among 713 patients, normal glucose tolerance (NGT) was diagnosed in 139 (19.5%), IGT in 252 (35.3%), and DM in 322 (45.2%). HCC developed in 81 patients over a median follow-up period of 42.0 months (interquartile range, 20.5–66.5 months): NGT, 9.3%; IGT, 12.3%; and DM, 9.6%. In patients with compensated cirrhosis (CTP class A; n = 415), neither IGT (19/157; HR, 1.740; P = 0.191) nor DM (22/173; HR, 1.784; P = 0.163) conferred a higher risk for development of HCC. Among patients with decompensated cirrhosis (CTP class B and C; n = 298), both IGT (12/95; HR, 1.603; P = 0.376) and DM (15/149; HR, 1.337; P = 0.575) also did not have significant impact on development of HCC. However, multivariate study in total patients showed that old age [adjusted hazard ratio (aHR) = 1.043; 95% CI = 1.020–1.066; P < 0.001], male (aHR, 3.959; 95% CI = 1.894–8.275; P < 0.001), higher MELD score (aHR, 1.095; 95% CI = 1.033–1.161; P = 0.002) and higher FBG by OGTT (aHR, 1.005; 95% CI = 1.001–1.010; P = 0.018) were identified as independent predictors of devel-

opment of HCC. **Conclusion:** Although newly diagnosed IGT and DM by OGTT is not a critical determinant for the development of HCC, higher FBG status carried an additional risk for HCC, and these patients should also be carefully monitored for HCC.

P-010

Changing Trends in Epidemiology and Clinical Outcomes of Korean Patients with Liver Cirrhosis: An Eight-Year Single Center Experience

Sunmin Kim¹, Eunae Cho¹, Chung Hwan Jun¹,
Seon Young Park¹, Chang Hwan Park¹, Hyun Soo Kim¹,
Sung Kyu Choi¹, Jong Sun Ryu¹

¹Chonnam National University Hospital, Gwanju, Korea

Background and Aims: In Korea, the most common cause of liver cirrhosis is chronic hepatitis B, followed by alcoholic liver disease and chronic hepatitis C. However, a recent study in Korea reported the prevalence of alcoholic cirrhosis to be up to 31%. Therefore, a nationwide survey of the current epidemiological status of liver cirrhosis in Korean patients is

greatly needed. **Method:** This was a retrospective cohort study of consecutive patients with cirrhosis who visited the Chonnam National University Hospital from 2008 to 2015. Baseline characteristics, complications, and mortality were evaluated. **Results:** This study included 1,336 cases of liver cirrhosis, 37.9% of which were due to hepatitis B (n = 506), 35.9% due to alcoholic liver disease (n = 480), and 11.6% due to hepatitis C infection (n = 155). Of patients who visited our institution in 2008, the proportion of patients with cirrhosis associated with alcoholic liver disease was 23.2%, which increased to 43.9% in 2015. The proportion of patients with hepatitis B was 53.7% in 2008 and dropped to 27.2% in 2015. The proportion of hepatitis C patients was 12.6% in 2008 and 13.3% in 2015. The most common complication observed was ascites (19.1%, n = 256), followed by variceal hemorrhage (14.4%, n = 193) and hepatocellular carcinoma (11.6%, n = 155). The percentage of Child-Pugh class C in alcoholic liver cirrhosis patients was 4.5% in 2008, which rose to 33.5% in 2015. Patients affected by hepatitis B and C, had increased occurrence rates of complications (15.7% to 38.3%, 8.3% to 43.5%, respectively). **Conclusion:** The progression status and complication rates in patients with alcoholic liver cirrhosis have shown a worsening tendency. A better understanding of trends in liver cirrhosis-related morbidity and mortality may be instrumental in steering future healthcare policies.

Table 1. Clinical characteristics of enrolled patients (for Abstract no P-010)

	2008 (n = 96)	2009 (n = 151)	2010 (n = 201)	2011 (n = 203)	2012 (n = 143)	2013 (n = 165)	2014 (n = 205)	2015 (n = 173)
Age(years)	56.91±10.73	57.85±11.38	58.94±11.24	60.55±11.43	58.89±11.28	59.59±11.32	59.73±10.57	60.33±12.10
Male, n(%)	58 (60.4%)	91 (60.3%)	122 (60.7%)	125 (61.6%)	104 (72.7%)	127 (71.8%)	147 (71.7%)	107 (61.8%)
Etiology								
Alcohol	22 (22.9%)	36 (23.8%)	48 (23.9%)	66 (32.5%)	66 (46.2%)	85 (51.5%)	81 (39.5%)	76 (43.9%)
HBV	52 (54.2%)	77 (51.0%)	98 (48.8%)	78 (38.4%)	39 (27.3%)	42 (25.5%)	74 (36.1%)	47 (27.2%)
HCV	12 (12.5%)	16 (10.6%)	30 (14.9%)	26 (12.8%)	11 (7.7%)	12 (7.3%)	25 (12.2%)	23 (13.3%)
Others	10 (10.4%)	22 (14.5%)	25 (12.5%)	33 (16.4%)	27 (18.9%)	26 (15.8%)	25 (12.2%)	27 (15.7%)
CPT score (mean)	5.61±1.04	5.58±1.18	5.65±1.28	5.78±1.36	6.63±1.74	6.65±2.10	6.21±1.52	6.55±1.85
A	81 (84.4%)	129 (85.4%)	168 (83.6%)	160 (78.8%)	81 (56.6%)	104 (63%)	138 (67.3%)	103 (59.5%)
B	14 (14.6%)	19 (12.6%)	28 (13.9%)	35 (17.2%)	53 (37.1%)	37 (22.4%)	58 (28.3%)	55 (31.8%)
c	1 (1.0%)	3 (2.0%)	5 (2.5%)	8 (3.9%)	9 (6.3%)	24 (14.5%)	9 (4.4%)	15 (8.7%)
MELD score (Modified)	10.46±3.88	10.12±5.31	10.34±4.72	10.33±4.62	12.51±5.93	13.31±6.80	10.90±5.25	12.43±6.30
Complication								
Ascites	6 (6.2%)	8 (5.3%)	22 (11.0%)	29 (14.2%)	42 (29.4%)	33 (20.0%)	60 (29.2%)	56 (32.3%)
Varix bleeding	9 (9.4%)	10 (6.6%)	13 (6.5%)	24 (11.8%)	40 (28.0%)	34 (20.6%)	28 (13.7%)	35 (20.2%)
HCC	3 (3.1%)	10 (6.6%)	14 (7.0%)	25 (12.3%)	10 (7.0%)	20 (12.1%)	28 (13.7%)	38 (22.0%)
encephalopathy	0 (0.0%)	2 (1.3%)	4 (2.0%)	4 (2.0%)	7 (4.9%)	20 (12.1%)	10 (4.9%)	12 (6.9%)
Others	7 (7.2%)	6 (4.0%)	11 (5.5%)	7 (3.5%)	5 (3.5%)	14 (8.5%)	10 (4.9%)	22 (12.7%)
Cause of death								
Varix bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.0%)	1 (0.7%)	4 (2.4%)	0 (0.0%)	7 (4.0%)
Hepatic failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.7%)	4 (2.4%)	2 (1.0%)	2 (1.2%)
Others	1 (1.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.7%)	1 (0.6%)	1 (0.5%)	5 (2.9%)

P-011

Comparing Clinical Patterns of Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease and Hepatitis B

Benjamin Wei Rong Tay¹, Yi Qing Tey²,
John Shao Rong Mok¹, Alfred Wei Chieh Kow³,
Glenn Kunnath Bonney³, Poh Seng Tan¹,
Yock Young Dan^{1,2}, Daniel Qingyao Huang¹

¹Division of Gastroenterology and Hepatology,
National University Health System, Singapore,

²Department of Medicine, Yong Loo Yin School of
Medicine, National University of Singapore, Singapore,

³Division of Hepatobiliary Surgery, National University
Health System, Singapore

Background: Hepatocellular carcinogenesis is a complex multifactorial process with resultant tumour heterogeneity manifesting as diverse clinical phenotypes. Current availability of information on HCC in Asian non-alcoholic fatty liver disease (NAFLD) does not mirror its increasing regional incidence. We aim to assess clinical features of patients with NAFLD-related HCC (NAFLD-HCC) and compare them to those of hepatitis B virus (HBV)-related HCC. **Methods:** Our retrospective cohort analysis compared clinical features of 262 HCC patients with either NAFLD (117) or HBV (117) diagnosed from 2008 to 2017. Assessment of response to treatment was evaluated using mRECIST criteria. 1:1 Propensity matching was performed before comparing the outcome measures of survival, response to initial treatment, recurrence, progression and time to progression. **Results:** Compared to HBV, HCC in NAFLD patients was significantly larger, had increased vascular invasion and was detected outside specific surveillance. NAFLD-HCC also showed significantly lower incidence of hypervascularity on imaging. Cirrhosis and portal hypertension were present in more NAFLD-HCC patients compared to HBV-HCC. Despite matching for tumour size, nodule number, vascular invasion and BCLC stage, survival was significantly shorter in patients with NAFLD-HCC (median survival 38 months compared to 131 months; P less than 0.001) with poorer response to initial treatment. **Conclusion:** NAFLD-HCC is often detected at a later tumour stage than HBV-HCC, with poorer survival and response to initial treatment. The way ahead will be to identify patients with NAFLD who require tighter surveillance and management.

P-012

Impact of On-Treatment Intermediate Endpoints on the Risk of Hepatocellular Carcinoma in HBeAg-Positive Chronic Hepatitis B Patients

Young-Suk Lim¹, Jonggi Choi¹, Gi-Ae Kim²

¹Asan Medical Center, University of Ulsan College
of Medicine, Korea, ²Kyung Hee University School of
Medicine, Korea

Alanine aminotransferase (ALT) normalization, virological response (VR), and HBeAg seroclearance are intermediate surrogate endpoints that are commonly used to monitor treatment responses in HBeAg-positive chronic hepatitis B (CHB) patients. However, the impact of these intermediate endpoints on the risk of hepatocellular carcinoma (HCC) in patients under highly-potent antiviral treatment remains unclear. We included a total of 2,630 HBeAg-positive CHB patients who initiated treatment with entecavir or tenofovir disoproxil fumarate at a tertiary hospital in Korea between 2007 and 2016, and analyzed the risk of HCC and death/transplantation. Normal ALT was defined as ≤ 25 U/L for female and ≤ 35 for male. We defined VR as serum HBV DNA < 15 IU/mL. The mean age of the patients was 45.1 years, 65.1% were male, and 38.7% had cirrhosis. During median follow-up period of 5.1 years with continued treatment, 216 patients developed HCC. ALT normalization was associated with a significantly lower risk of HCC by landmark analyses at 1-year and 2-years of treatment ($P < 0.001$ for all). By 2-year landmark analysis, neither of VR or HBeAg seroclearance was not associated with a significantly lower risk of HCC ($P = 0.97$ and $P = 0.13$, respectively). On-treatment ALT normalization was independently associated with a significantly lower risk of HCC (adjusted hazard ratio [aHR] = 0.44) by multivariable time-dependent Cox analysis. **Conclusions:** In HBeAg-positive CHB patients under treatment with highly-potent antiviral agents, ALT normalization was the sole on-treatment surrogate endpoint that was independently associated with lower risk of HCC, whereas VR and HBeAg seroclearance observed during treatment were not predictive of HCC development.

Diagnosis and Liver Imaging / Epidemiology and Surveillance / Miscellaneous

P-013

Development of Colorectal Cancer Predicts Increased Risk of Subsequent Hepatocellular Carcinoma in Patients with Alcoholic Liver Disease

Won Kim¹, Dongjae Jeong², Yong Jin Jung¹,
Jin-Wook Kim²

¹Seoul Metropolitan Government Boramae Medical
Center, Korea, ²Seoul National University Bundang
Hospital, Korea

Alcohol increases the risk of both hepatocellular carcinoma (HCC) and colorectal neoplasia. In this hospital-based case-control and retrospective cohort study, we sought to determine whether development of colorectal neoplasia increases the risk of HCC in patients with alcoholic liver disease (ALD). In the phase I case-control analysis, the association between history of colorectal cancer (CRC) and HCC development was assessed in 1659 patients with ALD by logistic regression modeling. In the phase II retrospective cohort analysis, the relative risk of HCC development was compared in 1184 ALD patients with respect to the history of CRC by a Cox model. The history of CRC was significantly associated with HCC in the case-control analysis (adjusted odds ratio, 1.82; CI, 1.06, 3.15; P less than 0.05). ALD patients with CRC had higher risk of developing HCC compared to those without CRC (adjusted hazards ratio, 5.48; CI, 1.63, 18.36; P, 0.006) in the cohort analysis. Presence of CRC, liver cirrhosis, elevated baseline alpha-fetoprotein level, and low platelet counts were independent predictors of HCC development in ALD patients. Patients with history of CRC had an increased risk of HCC in both cirrhotic (HR, 3.76; CI, 1.05, 13.34; P, 0.041) and non-cirrhotic (HR, 23.46; CI, 2.81, 195.83; P, 0.004) ALD patients. In conclusion, ALD patients with CRC are at increased risk of developing HCC.

P-014

Incidence of Hepatocellular Carcinoma Development in Cirrhotic Patients Has Not Been Decreased During Past 10 Years; A Single Center Experience

Jeong Han Kim¹, Won Hyeok Choe¹, So Young Kwon¹,
Byung Chul Yoo¹

¹Konkuk University School of Medicine, Korea

Background and Aims: In hepatitis B endemic area, clinical implications of cirrhotic patients seems to be improved since oral antiviral agents were introduced. However, alcoholic cirrhosis is still not well controlled and direct acting antiviral agents for hepatitis C are recently introduced. Therefore, change of hepatocellular carcinoma (HCC) development rate should be evaluated and in Korea. **Methods:** Medical records of cirrhotic patients visited Konkuk University medical center were retrospectively reviewed. Study period was from year 2008 to year 2017. New HCC diagnosis in cirrhotic patients in each year was evaluated. **Results:** During 10 years, mean 773 patients were visited in each year. Most common etiology was hepatitis B (48.4% in 2008 and 47.1% in 2017) and alcohol was second (28.3% in 2008 and 31.7% in 2017). HCC development was occurred in 34 patients (6.2%) in 2008, 47 patients (6.8%) in 2009, 70 patients (8.4%) in 2010, 58 patients (6.3%) in 2011, 57 patients (6.9%) in 2012, 43 patients (6.7%) in 2013, 37 patients (5.8%) in 2014, 52 patients (6.2%) in 2015, 49 patients (5.6%) in 2016 and 84 patients (9.1%) in 2017. HCC developments of hepatitis B patients was 16 patients (6.1%) in 2008 and 46 patients (10.5%) in 2017, and that of alcohol patients were 6 patients (3.9%) in 2008 and 20 patients (6.8%) in 2017. **Conclusions:** Although antiviral therapy for hepatitis B has been successfully launched in Korea, incidence of HCC development in cirrhotic patients has not been decreased during 10 years. It seems because other reason such as alcohol and hepatitis C are still not controlled and there are underestimated patients. Larger scale study and more aggressive screening and treatment strategies are warranted.

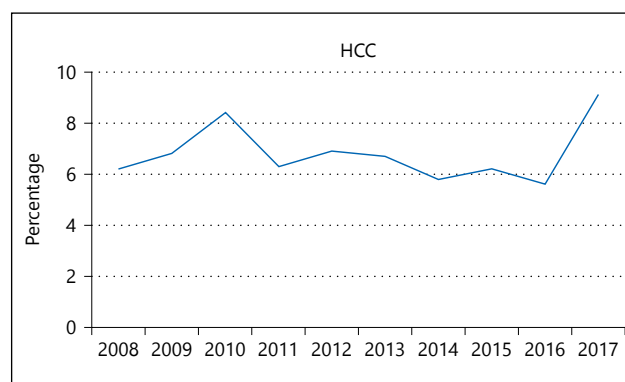


Fig. 1. (for Abstract no P-014).

P-015

Primary Adenosquamous Carcinoma of the Liver: A Case Report and Systematic Literature Review in Korean

Jae-Hui Kim¹, Ghilsuk Yoon¹, Hyung Jun Kwon²,
Sun-Jae Lee³, Man-Hoon Han⁴, An Na Seo¹

¹Department of Pathology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Korea, ²Department of Surgery, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Korea, ³Department of Pathology, Catholic University of Daegu School of Medicine, Daegu, South Korea, Korea, ⁴Department of Pathology, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Korea

Background: Primary Adenosquamous carcinoma (ASC) is one of rare variants of cholangiocarcinoma. Unfortunately, the detail characteristics and pathogenesis of this tumor have not been clarified yet due to limited data in the literature. **Methods:** We herein present a case of primary ASC in liver and a systematic review of the previous Korean literature. PubMed, Scopus, and Koreamed database searches were performed for case reports and case series of primary ASC in liver. **Results:** A 63 year old Korean man was referred to our hospital for a fever, chilling, and myalgia for 20 days, in February 3, 2019. An abdominopelvic computed tomography revealed a 5.6 cm ill defined mass with low density in the left lobe of liver and a distal intrahepatic duct dilatation. The patient underwent extended left hepatectomy. On gross examination, tumor had 8.0 cm diameter and light yellow color. The tumor showed infiltrative boundaries and invaded into the Glisson's capsule and adjacent serosa. Microscopic findings revealed a mixture of malignant glandular and squamous components and staged as pT3N1. The patient has been treated with adjuvant chemotherapy and monitored for 3 months post surgery. By full text review, eleven patients with primary ASC from 11 article from 1994 to 2016 were included. Median age was 63.0 years and 8 (72.7%) patients were male. Median tumor size was 6.75 cm and 6 patients (54.5%) had lymph node metastasis. **Conclusion:** Primary ASC occurs in the earlier age than conventional cholangiocarcinoma. It was commonly found lymph node metastasis and showed poor prognosis.

P-016

Mucinous Cystic Neoplasm of the Liver

Il-Young Park¹, Su-Hyun Jang¹, Gun-Hyung Na¹,
Ji-Heun Han²

¹Dept. of Surgery, Bucheon St. Mary Hospital, Catholic University of Korea, Korea, ²Dept. of Pathology, Bucheon St. Mary Hospital, Catholic University of Korea, Korea

Introduction: Mucinous cystic neoplasms (MCN-L) of the liver is a rare cystic tumor, which is difficult to differentiate from other cystic lesions of the liver. Preoperative exact diagnosis is also challenging by radiologic evaluation. MCN-L could be transformed to a malignant neoplasm in approximately 6% of cases. We present three cases of MCN-L. **Material and Methods:** The first case was a 63-year-old woman. A 3.8 cm lobulated mass in left liver was seen in CT scan and MRI. Left hepatectomy with cholecystectomy was performed. She remains alive without any recurrence on five year follow-up. Second case was a 62-year-old woman. She had no symptoms and the lesions had been noticed in a medical check-up. There were multiple cystic lesions, one of which presented as a 6.1x5.1 cm sized mass in segment IV. Liver partial resection was performed. She showed no signs of complication 2 months after operation. The last case was a 46-old-year woman who had felt abdominal distension and had a palpable mass in the right abdomen. In CT scan, there was a large cystic lesion in right sub-hepatic space (10x12x20 cm). Liver partial resection was performed. She is currently well on a monthly follow-up. **Results:** All patients were women. All lesions were in the left liver. Two cases were asymptomatic whereas one case showed mild symptoms. Pathologic findings showed tumor composed of cyst lined by columnar or cuboidal epithelial cells. Characteristically ovarian-type stroma which is immunoactive with estrogen receptors, was recognized. **Conclusions:** Diagnosis of MCN-L is relatively difficult to be confirmed by radiologic findings. However, MCN-L should be correctly diagnosed due to its malignant potential and prevented from improper treatments. Here, we report three cases of this rare tumor with clinical, radiological and pathological features to help accurate diagnosis and to offer proper treatment to patients.

P-017

A Rare Case of Cholangiocarcinoma Mimicking Pyogenic Abscess, Hepatic Echinococcal Cysts, and Metastases

Soo Hyung Ryu¹, Dong Hoon Lee¹, You Kyung Lee¹,
Bo Kyung Lee¹, Tae Young Park¹, Jeong Seop Moon¹

¹Inje University College of Medicine, Korea

Background: Cholangiocarcinoma is a rare cancer in the liver and a representative hypovascular tumor in the liver together with metastasis from other cancer. The pyogenic abscess is relatively common in immune compromised patient and echinococcal hepatic cyst is very rare. We experienced a very rare case of multiple hypodense masses with wall enhancement mimicking pyogenic liver abscess, echinococcal hepatic cyst, and metastasis, which was diagnosed as a cholangiocarcinoma by liver biopsy. **Case:** An 83-year-old man complaining of fatigue and poor oral intake visited our hospital. He had a medical history of cholecystectomy due to gall bladder perforation superimposed on acute cholecystitis 5 years ago. Hemoglobin level was 8.3 g/dl, WBC was in normal range, and CRP was elevated as 15.2 (0–0.8) mg/dl. He had an abnormal liver function test, especially albumin level was very low as 2.6 (3.5–5.2) g/dl. Tumor markers such as α -fetoprotein of 18.2 (0–10) ng/ml and CA19-9 of 88.3 (0–37) U/ml, protein induced by vitamin K absence or antagonist-II (PIVKA-II) of 64 (under 40) mAu/ml were abnormally increased. Both of hepatitis B surface antigen and surface antibody were negative. Hepatitis C antibody was also negative. Parasite specific antibody tests were all negative. Abdominal CT on visit revealed multiple sized hypodense masses with wall enhancement on the entire liver. Liver

dynamic MRI also showed similar findings with abdominal CT. After 10 days of antibiotic treatment, abdominal CT revealed no regression of masses in the entire liver. The ultrasound-guided biopsy for the mass revealed cholangiocarcinoma, which was consistent with adenocarcinoma, poorly differentiated, favor primary intrahepatic cholangiocarcinoma over metastatic adenocarcinoma in the liver. He died of heart failure at 18 admission days. **Conclusion:** We report a very rare case of intrahepatic cholangiocarcinoma mimicking pyogenic abscess, echinococcal hepatic cysts, and metastasis.

Molecular Pathogenesis and Pathology / Staging and Prognosis

P-018

Clinical Manifestation and Survival Outcomes According to Body Mass Index in Hepatocellular Carcinoma Patients; An Analysis of a Nationwide Cancer Registry Database

Jung Hwan Yu¹, Boram Cha¹, Young Ju Suh²,
Young-Joo Jin¹, Jin-Woo Lee¹

¹Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea, Korea, ²Department of Biomedical sciences, College of Medicine, Inha University, Incheon, South Korea, Korea

Background/Aims: Body mass index (BMI) is a value derived from the weight and height of individual, and is known to be closely related to the prognosis and mortality of various disease. The aims of our study is to evaluate the differences of post-treatment overall survival (OS) according to BMI in the patients with hepatocellular carcinoma (HCC), and to determine the meaning of BMI in these patients. **Methods:** The archived records of 10,578 HCC patients registered at the Korean Central Cancer Registry from 2008 through 2014 were retrospectively analyzed. In this registry, we selected Barcelona Clinic Liver Cancer (BCLC) 0, A, or B staged HCC patients (n = 4,977). **Results:** Among a total of 4,977 HCC patients, 151 (3.0%), 3,014 (60.6%), 1,607 (32.3%), and 205 (4.1%) patients had BMI of underweight, normal, overweight, and obesity, respectively. HCC patients showed good prognosis in the order of overweight, normal, obesity, and underweight. However, comparing normal and overweight in HCC patients after propensity score matching (PSM), there was no significant difference in survival rate between two groups (p = 0.153). In separate analyses of males and females, the overweight had better prognosis than the normal body weight in male (p = 0.014), but there was no



Fig. 1. (for Abstract no P-017).

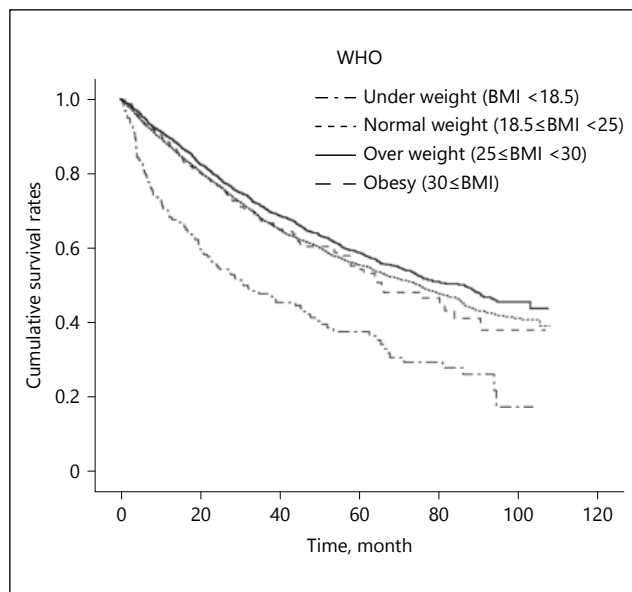


Fig. 1. (for Abstract no P-018).

significant difference in the OS between two groups in females ($p = 0.156$). Overweight patients showed better OS in TACE ($p = 0.039$) compared to normal body weight, but not in surgical resection ($p = 0.618$), radiofrequency ablation ($p = 0.553$), or sorafenib ($p = 0.241$). **Conclusions:** In patients with HCC of BCLC 0-B, overweight patients showed good prognosis, but there was no significant difference between overweight and normal body weight after PSM. However, unlike females, males showed better prognosis in the case of overweight, especially TACE treated patients. Our results carefully suggest that the meaning of normal BMI may be different between males and females in the patients with HCC.

P-019

The Relationship between Spleen Size and Prognosis in Patients Receiving Transarterial chemoembolization (TACE) for Hepatocellular Carcinoma (HCC)

Cheol Bae Ham¹, Nam Hee Kim², Won Sohn¹,
Yong Kyun Cho¹, Hong Joo Kim¹, Woo Kyu Jeon¹,
Byung Ik Kim¹

¹Kangbuk Samsung Hospital, Gastroenterology, Korea,
²Kangbuk Samsung Hospital, Preventive Healthcare Center, Korea

Introduction: Portal hypertension is an important prognostic factor in the treatment of HCC. Spleen size is one of the surrogate marker of portal hypertension and can be easily measured from computed tomography (CT) or magnetic resonance imaging (MRI). The purpose of this study was to evaluate

the effect of spleen size on clinical outcome in patients undergoing TACE for HCC. **Methods:** A retrospective data analysis was performed for a total of 386 patients who underwent TACE as first line therapy for HCC from January 2000 to June 2014. The Spleen index (SI) was used as representative value of spleen size or spleen volume ($SI (cm^3) = W(cm) * T(cm) * L(cm)$, W: width at the point of maximum width of the spleen, T: thickness at the midpoint of the section where W was determined, L: maximum cranio-caudal length of the spleen). Spleen index of enrolled patients was calculated using CT or MRI performed at the time of HCC diagnosis. We compared the overall survival (OS) and 5-year survival according to SI, which was divided into three groups (Group 1: $SI < 356.5 cm^3$, Group 2: $356.5 cm^3 - 576.4 cm^3$, Group 3: $SI > 576.4 cm^3$). **Results:** Multivariate analysis showed a statistically significant poor prognosis for OS in Group 3 (aHR 1.86, confidence interval [95% CI], 1.132–3.040, p value 0.014). Five-year OS rate was significantly lower in group 3 compared to group 1 (42.4% vs 60.4%) and group 2 (42.4% vs 62.2%). **Conclusions:** Spleen index reflecting spleen size or volume can be easily obtained from CT or MRI performed at HCC diagnosis without additional examination. Spleen index could be considered as a useful prognostic factor for patients with HCC undergoing TACE.

P-020

Portal Hypertension and Muscle Volume Loss in Early HCC Patients with Child-Pugh A, Who Are Treated Curatively

Atsushi Hiraoka¹, Kojiro Michitaka¹, Yoshifumi Suga¹,
Eiji Tsubouchi¹, Tomoyuki Ninomiya¹, Masashi Hirooka²,
Yoichi Hiasa²

¹Ehime Prefectural Central Hospital, Japan, ²Ehime University, Japan

Background/Aim: Esophagogastric varices (EGV) and muscle volume loss (MVL) are often complicated in chronic liver disease. This study aimed to evaluate the prognostic factors in patients with naive hepatocellular carcinoma (HCC) with Child=pugh A and within Milan criteria (MC), who were treated curatively. **Materials and Methods:** From 2000 to 2018, 1719 naive HCC patients were diagnosed and treated in our hospital. After exclusion of patients with past history of treatment against EGV or HCC beyond MC, Child-Pugh B and C, or those who were treated with non-curative methods, 457 were enrolled (70 years old, male 323, surgical resection 169). Portal hypertension was defined as F2 or more. MVL was defined with previously reported cut-off values (J Gastroenterol 2015). Prognostic factors were evaluated retrospectively. **Results:** Median survival time (MST) was 115.0 months in patients without PHT and MVL, 78.4 months in those only with PHT, 82.4 months in those only with MVL, and 68.1 months in those with both factors ($P < 0.001$). When prognostic factors were analyzed with Cox-hazard analysis with

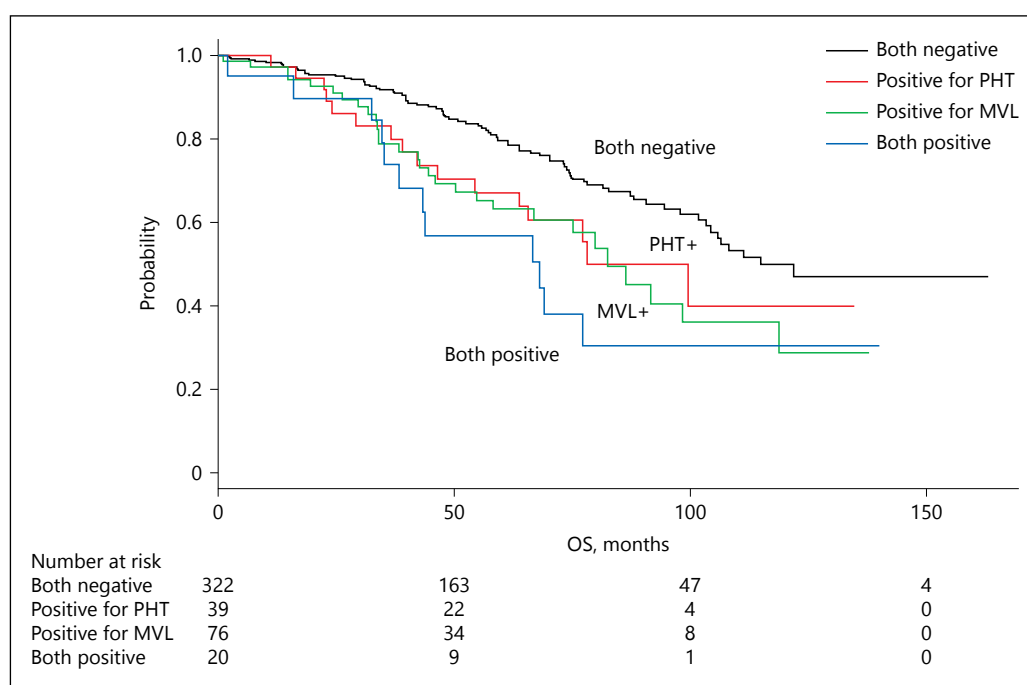


Fig. 1. (for Abstract no P-020).

gender, positive for hepatitis C virus, AFP (>100 ng/mL), surgical resection, MVL, PHT and albumin-bilirubin (ALBI) grade, ALBI grade 2 (HR 1.757, 95% CI: 1.251–2.468, $P = 0.001$) and MVL (HR 1.958, 95% CI: 1.354–2.832, $P < 0.001$) were significant prognostic factors. **Conclusion:** When PHT is treated approximately, influence of PHT to prognosis were small in naive HCC patients with good hepatic function (Child-Pugh A). ALBI grade 2 and MVL were significant prognostic factors. Assessment of muscle volume is important and strategies of intervention with nutrition and exercise should be established in near future.

P-021

Clinical Features and Risk Factors for Extrahepatic Metastasis of Hepatocellular Carcinoma After Radiofrequency Ablation: A Retrospective Study of 662 Patients in Two Tertiary Hospitals

Jae Hyun Yoon¹, Chung Hwan Jun¹, Sun Min Kim¹, Min Woo Jung^{1,2}, Chae Joon Lim¹, Sung Kyu Choi¹, Sung Bum Cho²

¹Chonnam National University Hospital, Korea, ²Hwasun Chonnam National University Hospital, Korea

Background: Risk factors for extrahepatic metastasis of hepatocellular carcinoma after radiofrequency ablation (RFA)

are not well known and guidelines for adequate surveillance for detection of extrahepatic metastasis (EHM) is still lacking.

Methods: We enrolled 661 patients who underwent RFA for initially detected hepatocellular carcinoma between 2006 and 2017. Computed tomography (CT), magnetic resonance imaging and position emission tomography were used for assessing tumor status with 3 to 6 months interval. **Results:** Among 661 enrolled patients, 44 patients (6.7%) were diagnosed to have EHM during mean follow-up period of 3.9 years. Mean age at the diagnosis of hepatocellular was 66.8 years old and 75.2% were male patients. The locations of EHM were as follows; intraabdominal lymph nodes (36.3%), bone (27.3%), lung (29.5%) and peritoneum (25.0%). Abdomen CT was used for diagnosis of EHM for 32 patients (72.7%) and chest CT for only 1 patient (2.3%) and median days of imaging interval before diagnosis of metastasis was 91 days. Thirty patients (79%) had increment of tumor marker (aFP or PIVKA) and mean days to EHM was 1236.6 days. At multivariate analysis, recurrence free survival less than 2 years (OR 2.44, $p = 0.02$), ratio of ablation zone by RFA and tumor size less than two (OR 3.33, $p = 0.01$) and aFP >400 IU/ml at 1st recurrence (OR 3.35, $p = 0.01$) were associated with high risk of EHM. **Conclusion:** Abdomen CT with follow-up interval of 90 days could detect most of EHM and role of chest CT was limited. Especially, patients with 1st recurrence free survival less than 2 years, ablated zone less than 2 times of tumor and aFP level higher than 400 IU/mL at 1st recurrence must be closely observed for risk of EHM.

Table 1. Univariate and multivariate analysis of factors associated with extrahepatic metastasis (for Abstract no P-021)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
BCLC stage (0 vs. A or B)	2.93 (1.38–6.20)	0.003		
mUICC (0, 1 vs. 1, 2)	2.04 (1.04–3.96)	0.034		
Post-RFA complication (fever, abscess)	2.78 (1.31–5.92)	0.05		
Presence of recurrence	48.8 (6.68–356.63)	0.000		
1st recurrence free survival <2 years	2.88 (1.54–5.38)	0.001	2.31 (1.14–4.67)	0.019
Ratio of ablation zone and tumor size	0.44 (0.29–0.68)	0.000	0.43 (0.26–0.70)	0.001
Presence of tumoral thrombosis	2.57 (1.13–5.84)	0.024		
aFP >400 at 1st recurrence	4.52 (2.03–10.07)	0.000	4.15 (1.78–9.66)	0.001
Tumor stage at 1st recurrence	1.77 (1.25–2.51)	0.001		

P-022**Relationship between Hepatitis C Virus and Activated Interferon Signaling in Hepatocellular Carcinoma from TCGA data**Yoshinari Asaoka¹, Atsushi Tanaka¹¹Teikyo University School of Medicine, Japan

Background: Some clinical issues have raised the possibility that Hepatitis C virus (HCV) related Hepatocellular carcinoma (HCC) might have specific molecular features. However, no gene mutations, which are specific for HCV-related HCC, has been discovered. Recently, exhaustive analysis of genetic mutations in HCC has been carried out due to the development of sequencing technology, and the results are reported. In this study, we have sought the specific gene mutation or expression for HCV-related HCC using data of TCGA (The Cancer Genome Atlas). **Methods:** Pretreated data of genetic mutations and gene expressions from 364 HCC cases were downloaded from the GDAC Firehose browser (<https://gdac.broadinstitute.org>) and analyzed with software R. One or more cases harbored mutations of 14,728 genes and the expression of 20,500 genes could be analyzed. The proportion of each mutation and the expression of each gene were compared between 56 HCV-related HCC and 308 non-HCV-related HCC cases by Fisher's exact test and t test, respectively. The expression of interferon (IFN) stimulated genes (ISG) were analyzed between with and without each mutation of 14,782 genes by t test to discover gene mutations related to activated IFN signaling. **Results:** No significant gene muta-

tions were found in HCV-related HCC. Analyzing the gene expressions, ISG such as IFI27, IFI44, ISG15, MX1, HERC5, OAS2, and IFI44L were upregulated most significantly ($p < 10^{-7}$). In addition, the expressions of these ISG were also significantly elevated in cancers harboring JAK1 mutation. **Discussion:** It has been suggested that IFN/JAK signaling is activated in HCV-related HCC. Considering that gain-of-function mutations of JAK1 gene occur in HCC, it is possible that part of this signal activation may function as oncogenic and it may be a therapeutic target. **Conclusion:** The expressions of ISG were significantly activated in HCV-related HCC.

Treatment: Systemic, Targeted, Novel Target or Experimental Therapy

P-023

Impacts of Diabetes and Hypertension on Hepatocellular Carcinoma Patients Receiving Sorafenib

Jung-Ta Kao¹, Cheng-Yuan Peng¹, Hsueh-Chou Lai¹, Po-Heng Chuang¹

¹China Medical University Hospital, Taiwan

Background and Aim: Prognostic roles of diabetes and hypertension in sorafenib-treated hepatocellular carcinoma (HCC) remain unclear. The study aims to elucidate whether diabetes and hypertension affect sorafenib-treated HCC patients. **Methods:** From August 2012 to February 2018 at China Medical University Hospital, 733 sorafenib-treated HCC patients were enrolled and divided into: Group 4 (without diabetes and hypertension, n = 353), 2 (diabetes only, n = 91; 2a: oral hypoglycemic agents (OHA)-treated, n = 76; 2b: regular insulin (RI) plus neutral protamine hagedorn (NPH)-treated, n = 15), 3 (hypertension only, n = 194), and 4 (diabetes and hypertension, n = 105; 4a: OHA-treated, n = 91; 4b: RI plus NPH-treated, n = 14). We then assessed outcomes of each group. **Results:** Group 2 and 4 instead of 3 have longer overall survival (OS) than Group 1 (OS in Group 1 to 4: 7.70, 11.83, 8.80 and 11.43 months, respectively; 1 versus 2, p = 0.001; 1 versus 3, p = 0.237; 1 versus 4, p = 0.005). Both Group 2a and

2b have longer OS than Group 1 (1 versus 2a, 7.70 versus 10.80 months, p = 0.011; 1 versus 2b, 7.70 versus 21.87 months, p = 0.009), with longer progression-free survival in Group 2b than 2a (21.03 versus 5.67 months, p = 0.045). Compared with Group 1, Group 4a has longer OS (7.70 versus 12.60 months, p = 0.004), yet Group 4b has no significant OS benefit (7.70 versus 9.47 months, p = 0.505). **Conclusion:** Diabetes prolongs sorafenib-treated HCC patients' survival, while hypertension has no direct prognostic impact. Both OHA and RI plus NPH improve patients' prognosis, and RI plus NPH has better survival benefit than OHA but may be worsened by hypertension.

P-024

The Real-World Practice of Lenvatinib in Patients with Advanced Hepatocellular Carcinoma in Taiwan

Yen-Hao Chen¹, Yen-Yang Chen¹, Chih-Chi Wang¹, Yueh-Wei Liu¹

¹Kaohsiung Chang Gung Memorial Hospital, Taiwan

Background/Aim: Lenvatinib has been proved in the treatment of advanced hepatocellular carcinoma (HCC) recently. The current study was to evaluate the clinical outcome of lenvatinib in patients with HCC in Taiwan. **Methods:** From January 2014 to December 2018, we retrospectively reviewed the HCC database in Kaohsiung Chang-Gung Memorial Hospital, and 62 patients with advanced HCC who received lenvatinib were identified finally. Lenvatinib was given orally 10 mg once daily for most patients. Tumor

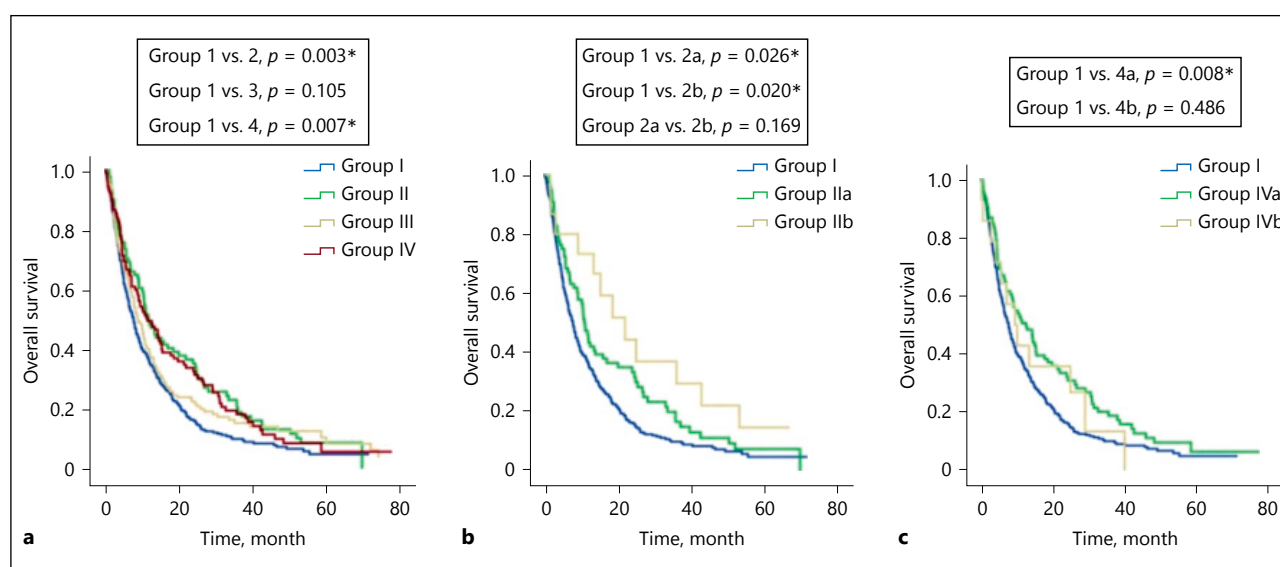


Fig. 1. Overall survival curves of (a) Group 1, 2, 3 and 4 (b) Group 1, 2a and 2b (c) Group 1, 4a and 4b. * A p-value below 0.05 indicates that two curves are statistically different (for Abstract no P-023).

Table 1. Characteristics of 62 patients with hepatocellular carcinoma receiving lenvatinib (for Abstract no P-024)

Characteristics	
Age	58 years old (34–79)
Sex	
Male	50 (81%)
Female	12 (19%)
Child-Pugh classification	
A	47 (76%)
B	15 (24%)
BCLC classification	
A	3 (5%)
B	5 (8%)
C	53 (85%)
D	1 (2%)
Viral hepatitis status	
Hepatitis B	32 (63%)
Hepatitis C	12 (19%)
Hepatitis B + C	1 (2%)
No	10 (16%)
Main portal vein thrombosis	
Yes	13 (21%)
No	49 (79%)
BCLC, Barcelona-Clinic Liver Cancer.	

assessment was performed using dynamic liver computed tomography (CT) or magnetic resonance imaging (MRI) every 4–12 weeks in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. **Results:** There were 62 patients with a median age of 58 years, including Child-Pugh A 47 patients and Child-Pugh B 15 patients. The lenvatinib treatment was defined as first line in 23 patients, second line in 21 patients, third line in 8 patient, and fourth line and later lines in 10 patients. Thirty-two patients had hepatitis B and twelve patients got hepatitis C; thirteen patients were found to have main portal vein thrombosis. Thirty-seven patients (60%) had history of previous sorafenib treatment before lenvatinib use. The treatment response was revealed to be partial response in 19 patients (31%), stable disease in 17 patients (27%), and progressive disease in 26 patients (42%). The median progression-free survival (PFS) was 3.4 months for all patients and 7.1 months for responders. The median overall survival (OS) was 9.2 months and 20.6 months for all patients and responders, respectively. Hepatitis B, hepatitis C, main portal vein thrombosis or previous sorafenib treatment were not prognostic factors of PFS and OS. **Conclusions:** In our clinical experience, the real-world study showed the efficacy of lenvatinib for advanced HCC patients.

P-025**The Efficacy and Safety of Lenvatinib for Advanced Hepatocellular Carcinoma Which Beyond REFLECT Study Indications in a Real-World Setting**Gong Li¹, Guangxin Li¹, Jiahong Dong¹¹Tsinghua University Affiliated Beijing Tsinghua Changgung Hospital, China

Background/Purpose: Lenvatinib was non-inferior to sorafenib in a phase 3 trial (REFLECT trial) of advanced hepatocellular carcinoma. However, patients with the liver tumor volume greater than 50% of the whole liver and with main portal vein tumor thrombus, that often exists in clinical practice, excluded in REFLECT trial. This study aimed to examine the safety and efficacy of lenvatinib to the patients which beyond REFLECT study indications in a real-world setting. **Methods:** This was a retrospective, single-center, observational study, that observed unresectable hepatocellular carcinoma patients with the tumor accounted for more than 50% of the liver volume or with main portal vein tumor thrombus. Participants were observed for at least 12 weeks. Therapeutic effect was determined using the modified Response Evaluation Criteria In Solid Tumors (m-RECIST) at the 12th week. **Results:** 21 patients were observed in this study. Fatigue, leukopenia and dysphoria were the most frequent AEs. Leukopenia, hand-foot skin reaction and decreased appetite were the most frequent AEs which were higher than Grade 2. 7 of these patients had elevated Child-Pugh scores and 3 of whom increased from Child-Pugh A to B. All of the AEs could be controlled by appropriate dose reduction, interruption, and symptomatic treatment. No liver function failure occurred. The probability of tumor marker (AFP or PIVKA-II) decline was 100% and 60% at 1 month and 3 months after administration, respectively. In the m-RECIST evaluation at the 12th week, 0, 7, 7, and 7 patients had achieved complete response, partial response, stable disease, and progressive disease, respectively. The objective response rate was 33.3%. All the patients were alive. **Conclusion:** Lenvatinib treatment could be accomplished with safety and good response to the patients which beyond REFLECT study indications in a real-world setting.

P-026

Which Is the First Choice for the Treatment of Advanced HCC, Lenvatinib or Sorafenib?

Takuya Adachi¹, Kazuhiro Nouse¹, Atsushi Oyama¹, Nozomu Wada¹, Masahiro Sakata¹, Tetsuya Yasunaka¹, Hideki Onishi¹, Hidenori Shiraha¹, Akinobu Takaki¹, Hiroyuki Okada¹

¹The University of Okayama, Japan

Background/Aim: Sorafenib and lenvatinib are the first-line therapies for advanced HCC and could be used only in patients with Child-Pugh A. Therefore, the extent of deterioration of liver function by these drugs is a matter of interest in terms of considering the second-line therapy. The aim was to examine effectiveness and changes of liver function by these drugs. **Method:** We examined prospectively the treatment effect and the changes of liver function in 27 and 80 HCC patients who were treated with lenvatinib and sorafenib as first-line therapies, respectively. **Result:** Liver function before lenvatinib treatment was Child-Pugh score 5, 6, and 7-, in 44%, 44% and 12% of the patients, respectively. The best treatment effects evaluated by mRECIST were CR, PR, SD and PD in 4%, 19%, 40% and 36%. Child-Pugh scores at the time of PD were 5, 6 and 7-, in 33%, 27% and 40%. The patients with Child-Pugh score 5 at PD could continue lenvatinib (40%) or change sorafenib (60%). However, the treatments with Child-Pugh score 6 at PD were BSC (50%), sorafenib (25%) or continued lenvatinib (25%), and with Child-Pugh 7- at PD were BSC (67%), HAIC (17%) or continued lenvatinib (17%). In patients treated with sorafenib between 2013 and 2016, 58%, 29% and 14% were Child-Pugh score 5, 6, and 7-. The best treatment effects were PR, SD and PD in 8%, 32% and 61%. Child-Pugh score at PD were 5, 6 and 7-, in 52%, 12% and 37%. Therefore, 64% of the patients treated with sorafenib theoretically could use other molecular target drugs as second-line therapy. **Conclusion:** Objective response rate of lenvatinib was higher than that of sorafenib; however, they were almost equal in respect of the deterioration of liver function at PD. These results indicate that both drugs have an equal chance of sequential therapy.

P-027

Effectiveness of Dose Reduction of Sorafenib on HCC Treatment: A Real Life Multicenter Data Analysis

Jeong Won Jang¹, Kwon Yong Tak¹, Pil Soo Sung¹, Hee Chul Nam¹, Jong Young Choi¹, Seung Kew Yoon¹, Jin Mo Yang¹, Chang Wook Kim¹, Hee Yeon Kim¹, Seung Won Lee¹, Hae Rim Lee¹, U Im Chang¹, Do Seon Song¹, Jung Hyun Kwon¹, Sun Hong Yoo¹, Sang Wook Choi¹, Myeong Jun Song¹, Seok Hwan Kim¹

¹Catholic University of Korea, Korea

Currently, there is no guide for sorafenib dosing. This study is a multicenter, retrospective, real-life, cohort study aiming to evaluate whether sorafenib dosing would affect survival. 782 patients treated with sorafenib from 6 centers were evaluated for dosing. Sorafenib dose was recorded daily with patients under regular followed-up regardless of adverse event. Patients were analyzed based on dose modification. Primary outcomes were overall survival and time to progression. The study included patients with sorafenib initiation date from September 3, 2008 to July 5, 2018, with median follow-up of 155 days. Median survival was 5.2 months. In multivariate analysis, dose reduction had significant benefit on overall survival ($p = 0.019$) and progression free survival ($p = 0.034$). Subgroup analysis showed median survival of 3.23 months in 800–600 mg group and 3.77 months in 800–400 mg group ($p = 0.369$). Risk for both hand-foot syndrome ($p = 0.049$), and drug discontinuation due to adverse-effect ($p = 0.003$) were higher in 800–600 mg group. Dose reduction to 200 mg significantly reduced overall survival ($p = 0.014$) and progression-free-survival ($p = 0.025$). Dose reduction significantly elongated medication duration ($p = 0.000$). Cumulative dose significantly rose with dose reduction ($p = 0.00$). In subgroup analysis, 800–400 mg group had significantly longer duration ($p = 0.00$) and higher cumulative dose ($p = 0.02$) than 800 mg maintained group. Subgroup analysis showed consistent result in good-responders. In HCC patients treated with sorafenib, dose reduction lead to longer overall survival and progression-free survival. Dose reduction reduces daily intake, however increases patient tolerance leading to longer duration and higher cumulative dose, ultimately improving survival. Based on our data, dose reduction to 400 mg than 600 mg is recommended for patients initially taking 800 mg. There was no meaningful difference in time-to-progression, but significantly lesser patients had hand-foot syndrome, and discontinued Sorafenib due to adverse-events. Regardless of initial dose, dose reduction to 200 mg is not recommended.

P-028

Anti-Tumor Effect of Ginsenoside Rh2 and Rg5 in Xenograft Hepatoma Animal Model -Comparison with Sorafenib-

Jae Young Jang¹, Sukmin Kang¹, Soung Won Jeong¹,
Young Chang¹, Jeong-Ju Yoo³, Sae Hwan Lee²,
Sang Gyune Kim³, Young Seok Kim³, Hong Soo kim²,
So Young Jin⁴

¹Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea, ²Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea, ³Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea, ⁴Department of Pathology, Soonchunhyang University College of Medicine, Seoul, Korea

Background and Aim: We investigate therapeutic effects of ginsenoside Rh2 and Rg5 using animal & cell models of liver cancer comparing with sorafenib. **Methods:** Huh7 & huh7.5.1 cells were harvested from 2-D petri-dish cultures by treatment with trypsin. These cells cultured in 1.5 % soft agarose gels for 10–14 days. After 10–14 days, 3-D hepatic structure was formed and treated with ginsenoside Rh2 (100, 200 uM) and Rg5 (10, 50, 100 uM) for 72 h. Comparison between 2-D and 3-D models was done with microscopic and protein analysis. Hep3b cells (2×10⁵) in matrigel were suspended in 100 µl of PBS and then injected into the flanks of BALB/C nude mouse at 6 weeks. Sorafenib (10 mg/kg), ginsenoside Rh2 (100 uM) and Rg5 (100 uM) was injected to intra-peritoneum twice a week. After 4 weeks, all mice were sacrificed and tumor tissue was collected. The tissue was stained with hematoxylin and eosin and histological evaluation was conducted by blindly pathologist. Area of necrosis and vascular change in tumor tissue was calculated using the lasso tool to encircle the area

in ZEN 2011 Imaging Software. **Results:** Both ginsenoside Rh2 and Rg5 induced cell necrosis in liver cancer cell lines, and more necrosis occurred in 2D models. The expression of cleaved PARP protein was increased in both 2D and 3D cells with exposure to ginsenoside Rh2 and Rg5. The hepatocellular carcinoma was confirmed in HCC mouse models by H&E stain. Increased necrosis and telangiectasia were observed in mice treated with Rh2, Rg5 and sorafenib compared to control mouse. **Conclusions:** Our findings provide insight into the use of xenograft mouse as models of HCC and ginsenoside Rh2 & Rg5 might be a potential treatment candidate of liver cancer.

P-029

Genomic and Clinical Significance of the Thioredoxin System and TXNDC Family in Hepatocellular Carcinoma

Hyuk Soo Eun^{1,2}, Sang Ok Jung¹, Min Ji Cho¹,
Woo Sun Rou^{1,2}, Seok Hyun Kim^{1,2}, Byung Seok Lee^{1,2}

¹Department of Internal Medicine, Chungnam National University Hospital, 282, Munwha-ro, Jung-gu, Daejeon, 34952, Republic of Korea, Korea, ²Department of Internal Medicine, School of Medicine, Chungnam National University, 266, Munwha-ro, Jung-gu, Daejeon, 35015, Republic of Korea, Korea

Background/Aims: Oxidative stress occurs due to the excessive generation of cellular reactive oxygen species and antioxidant system dysfunction. The thioredoxin (TXN) system and TXN-domain-containing protein (TXNDC) family form networks maintaining the cellular reducing environment. Recently, the importance of these genes in the tumor environment has been emphasized. To investigate the clinical significance of TXNs and TXNDC family members in HCC **Methods:** Genomic data from 367 hepatocellular carcinoma

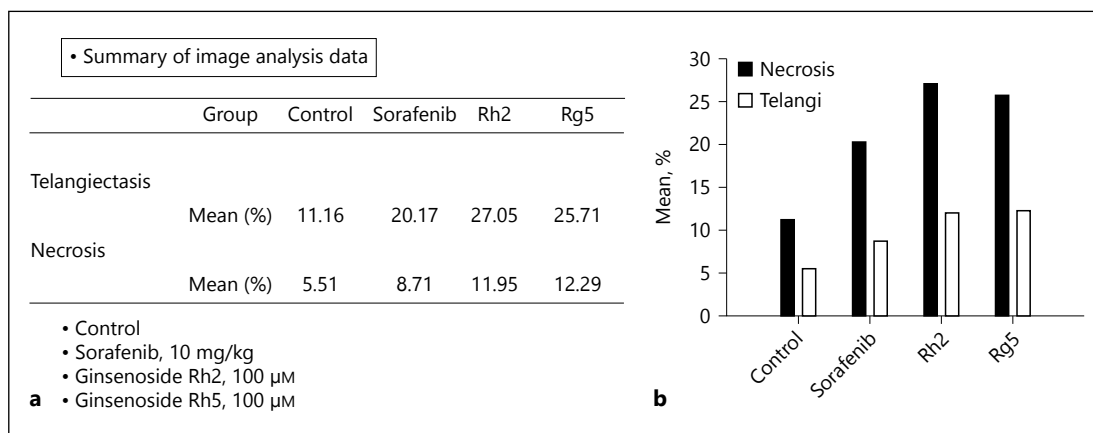


Fig. 1. Area of necrosis and vascular change in tumor tissue was calculated using the lasso tool to encircle the area in ZEN 2011 imaging Software (for Abstract no P-028).

(HCC) patients whom underwent hepatic resections were analyzed to determine genetic alterations in mRNA and protein levels between patients and healthy controls. In addition, functional enrichment and survival analyses were performed.

Results: HCC patients were shown to have the enhanced expression of TXN, TXNRD1, TXNDC7/9/14 mRNA and protein compared with that of controls. In accordance to the survival analyses, strong associations were found that patients with TXN, TXNRD1, and TXNDC1/7/9 alterations were proven to have poor prognosis in overall survival. Moreover, gene set enrichment analyses and network analyses revealed that positive correlations were found in mRNA expression of TXN, TXNRD1, and TXNDC7/9 genes with upregulation of the genes to tumor promoting genes, specifically mTORC1, E2F targets, and Myc targets. On the other hand, elevated expressions of TXNIP and TXNDC11 genes were correlated with suppression of the above tumor promoting genes. **Conclusions:** TXN system and TXNDC family gene panel obtained from the resected tissue of the HCC patients could be used to predict survival prognosis of HCC and these genes could be considered as potential therapeutic targets for improving HCC survival.

P-030

Cytochrome P450 4A11 Expression in Hepatocellular Carcinoma Cells

Hyuk Soo Eun^{1,2}, Sang Ok Jung¹, Min Ji Cho¹,
Woo Sun Rou^{1,2}, Seok Hyun Kim^{1,2}, Byung Seok Lee^{1,2}

¹Department of Internal Medicine, Chungnam National University Hospital, 282, Munwha-ro, Jung-gu, Daejeon, 34952, Republic of Korea, Korea, ²Department of Internal Medicine, School of Medicine, Chungnam National University, 266, Munwha-ro, Jung-gu, Daejeon, 35015, Republic of Korea, Korea

Background and Aim: Elevated cytochrome p450 (CYP) 4A gene expression has been linked to the aggravation of various cancers and affects various regulated metabolites. In hepatocellular carcinoma (HCC), the clinicopathological value of CYP4A has not yet been explored, although CYP4A is expressed at high levels in the liver. The goal of this study was to evaluate the clinicopathological value of CYP4A11 expression in HCC. **Methods:** We performed immunohistochemical analysis of CYP4A11 and correlated the results with clinicopathological features of HCC (n = 155). Western blotting and reverse transcription-polymerase chain reaction against CYP4A11 and CYP4A22 were also performed for 15 and 20 pairs of fresh-frozen primary HCC and non-neoplastic liver tissue, respectively. Moreover, we analyzed the underlying mechanism by comparing the high and low CYP4A11 mRNA expression groups using gene set enrichment analysis. **Results:** CYP4A11 expression level was higher in non-neoplastic hepatocytes than those in HCC cells (P < 0.001), and CYP4A11 expression positively correlated with favorable prognostic factors, including tumor size, histological grade, and

pathological tumor stage (P = 0.007, P = 0.005, and P = 0.007). Multivariate analysis revealed that CYP4A11 expression was an independent prognostic factor of overall and disease-free survival (P = 0.002 and P = 0.033). Based on gene set enrichment analysis, high CYP4A11 mRNA expression negatively correlated with the expression of cell cycle-related genes. **Conclusion:** These findings support the notion that CYP4A11 expression is a favorable prognostic factor of HCC and suggest potential predictive diagnostic and prognostic roles of CYP4A11 expression in HCC.

P-031

Comprehensive Analysis of Cytochrome P450 Family 4 Gene Expression in Hepatocellular Carcinoma

Hyuk Soo Eun^{1,2}, Sang Ok Jung¹, Min Ji Cho¹,
Woo Sun Rou^{1,2}, Seok Hyun Kim^{1,2}, Byung Seok Lee^{1,2}

¹Department of Internal Medicine, Chungnam National University Hospital, 282, Munwha-ro, Jung-gu, Daejeon, 34952, Republic of Korea, Korea, ²Department of Internal Medicine, School of Medicine, Chungnam National University, 266, Munwha-ro, Jung-gu, Daejeon, 35015, Republic of Korea, Korea

Background/Aims: Cytochrome P450 family 4 (CYP4) enzymes are known as microsomal omega (ω)-hydroxylases that metabolize fatty acids, eicosanoids, vitamin D and carcinogens. Thus, CYP4 enzymes may influence tumor development and progression. The aim of this study was to evaluate the CYP4 expression profile in hepatocellular carcinoma (HCC) and its clinical relevance. **Materials and Methods:** We obtained CYP4 mRNA expression data for 377 HCC cases from The Cancer Genome Atlas (TCGA) cohort and performed Kaplan-Meier survival, Gene Ontology functional enrichment, and gene set enrichment (GSEA) analyses. In addition, we evaluated the level of CYP4F2 protein expression in matched pairs of HCC and non-tumor tissue samples and correlated the results with the clinicopathological characteristics of HCC (n = 113). **Results:** HCC survival analyses indicated better overall survival in patients with high CYP4F2, CYP4F12 and CYP4V2 mRNA expression levels; the results for histologic grade and Tumor-Node-Metastasis stage supported these data. GSEA revealed high levels of CYP4F2, CYP4F12, and CYP4V2 mRNA expression to be negatively correlated with expression of cell cycle-related genes. CYP4F2 protein expression was higher in non-neoplastic liver tissue than in HCC tissue and positively correlated with favorable pathological tumor stage (I versus II-IV) (p = 0.022) and was a good independent prognostic factor for overall survival (p = 0.004). **Conclusion:** These findings demonstrate that the expression levels of genes CYP4F2, CYP4F12 and CYP4V2 are favorable prognostic factors in HCC and suggest the potential predictive diagnostic and prognostic roles of CYP4F2, CYP4F12 and CYP4V2 gene expression in HCC.

Treatment: Surgical Resection and Transplantation

P-032

Factors and Models for Predicting Liver-Related Morbidity in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma

Jonggi Choi¹, So-hyun Kim¹, Danbi Lee¹, Ju Hyun Shim¹, Young-Suk Lim¹, Han Chu Lee¹, Young-Hwa Chung¹, Yung-Sang Lee¹, Kang Mo Kim¹

¹Asan Medical Center, University of Ulsan College of Medicine, Korea

Aims: To seek predictive factors and to build predictive model for liver-related morbidity after liver resection for HCC.

Method: A total of 1,565 patients who underwent liver resection for HCC at Asan Medical Center, were retrospectively analyzed. Post-hepatectomy biochemical dysfunction (PHBF) was defined as increased INR >1.5 or hyperbilirubinemia >2.9 mg/dL on or after postoperative day (POD) 5. Definition of post-hepatectomy liver-related morbidity included PHBF, ascites requiring diuretics or drainage procedures, hepatic encephalopathy, rescue liver transplantation, and death within 90 days after operation. **Results:** 1,258 patients were men (80.4%) with a mean age of 58.3 years. Major etiology of underlying liver disease was chronic hepatitis B (80.8%). Patients with cirrhosis comprised of 37.9% of patients. 790 (50.5%) underwent right hepatectomy and 271 (17.3%) received left

hepatectomy. Segmentectomy was performed in 272 (17.4%) patients and 85 (5.4%) received bisegmentectomy. Eighty-three (5.3%) patients developed PHBF. Post-operative ascites occurred in 51 (3.3%) patients. Two patients experienced liver failure subsequently underwent rescue liver transplantation. A total of 13 mortality occurred within 90 days after operation, of which 4 patients died within 30 days. Male, cirrhosis, major resection, platelet $\leq 150,000$, serum albumin level ≤ 3.5 g/dL, and INR were selected as factors for predicting post-operative liver-related morbidity in the training cohort with AUROC of 0.737 and 0.740 in the training and test set, respectively.

Conclusion: A point-based prediction model with points assigned for sex (male: 3), cirrhosis (2), major resection (2), platelet $\leq 150,000$ (1), serum albumin ≤ 3.5 g/dL (2), and INR (INR <1.0: 0, 1.0 $\leq$ INR <1.1: 1, 1.1 $\leq$ INR <1.2: 2, and INR ≥ 1.2 : 5) enabled predictive risk for liver-related morbidity after liver resection for HCC.

P-033

Salvage Hepatectomy for Recurrent Hepatocellular Carcinoma After Radiofrequency Ablation and/or Transcatheter Arterial Chemoembolization: A Propensity Score-Matched Analysis

Tatsuya Orimo¹, Toshiya Kamiyama¹, Hirofumi Kamachi¹, Shingo Shimada¹, Akihisa Nagatsu¹, Yo Asahi¹, Akinobu Taketomi¹

¹Hokkaido University Graduate School of Medicine, Japan

Aim: We aimed to evaluate the short- and long-term surgical outcomes of salvage hepatectomy for recurrent hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) and/or transcatheter arterial chemoembolization (TACE). **Methods:** We reviewed the surgical outcomes of 90 recurrent HCC patients after RFA and/or TACE (salvage group) and 490 HCC patients without preoperative treatment (primary group). We performed 1:1 propensity score matching (PSM) between the two groups and matched 87 patients in each group. **Results:** Before PSM, salvage group was pathologically more advanced than primary group. After PSM, there were no significant differences in the clinicopathological features between the groups. The outcomes of propensity score matched groups were compared and there was no statistically significant difference between the two groups regarding perioperative outcomes and survival. Univariate and multivariate analyses of propensity score-matched HCC patients revealed that stage, tumor size, differentiation, and portal vein invasion were independent prognostic factors for survival. Preoperative RFA and/or TACE was not a prognostic factor in a propensity score-matched cohort. **Conclusions:** The short- and long-term surgical outcomes of the primary and salvage groups were similar under the matched clinico-

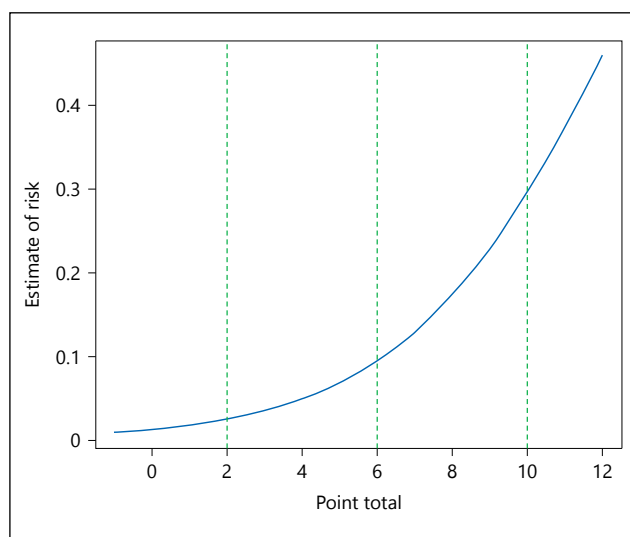


Fig. 1. Area of necrosis and vascular change in tumor tissue was calculated using the lasso tool to encircle the area in ZEN 2011 imaging Software (for Abstract no P-032).

pathological background. Salvage hepatectomy might be an acceptable treatment for recurrent HCC patients after RFA and/or TACE.

P-034

The Real Impact of Bridging or Downstaging on Survival Outcomes after Liver Transplantation for Hepatocellular Carcinoma

Sunyoung Lee¹, Gi-Won Song², Kyoung Won Kim²

¹Severance Hospital, Yonsei University College of Medicine, Korea, ²Asan Medical Center, University of Ulsan College of Medicine, Korea

Background/Aims: Liver transplantation (LT) is the optimal treatment for hepatocellular carcinoma (HCC) in selected patients with cirrhosis. We evaluated the long term

outcomes of patients who underwent LT with or without bridging or downstaging for HCC. **Methods:** This retrospective study included 896 LT recipients with HCC at a tertiary center between June 2005 and May 2015. Recurrence free survival (RFS), overall survival (OS), and their associated factors were evaluated. **Results:** The 5 year RFS in the full cohort of 896 patients was 82.4% and the 5 year OS was 85.3%. In patients with initial Organ Procurement and Transplantation Network (OPTN) T1 and T2, the 5 year RFS and OS did not significantly differ between LT groups with and without bridging (all $P \geq 0.05$). The 5 year RFS and OS of OPTN T3 patients with successful downstaging (SD) were not significantly different from those with OPTN T2 with primary LT ($P = 0.070$ and $P = 0.185$), but were significantly higher than in patients with OPTN T3 with downstaging failure and initial OPTN T1 or T2 with progression (all $P < 0.001$). In the multivariable analysis, pretransplant HCC status exceeding the Milan criteria (hazard ratio [HR], 3.55, $P < 0.001$ and HR, 2.40, $P < 0.001$), positron emission tomography positivity (HR, 2.27, $P < 0.001$ and HR, 2.45, $P < 0.001$) and microvascular invasion (HR, 3.24, $P <$

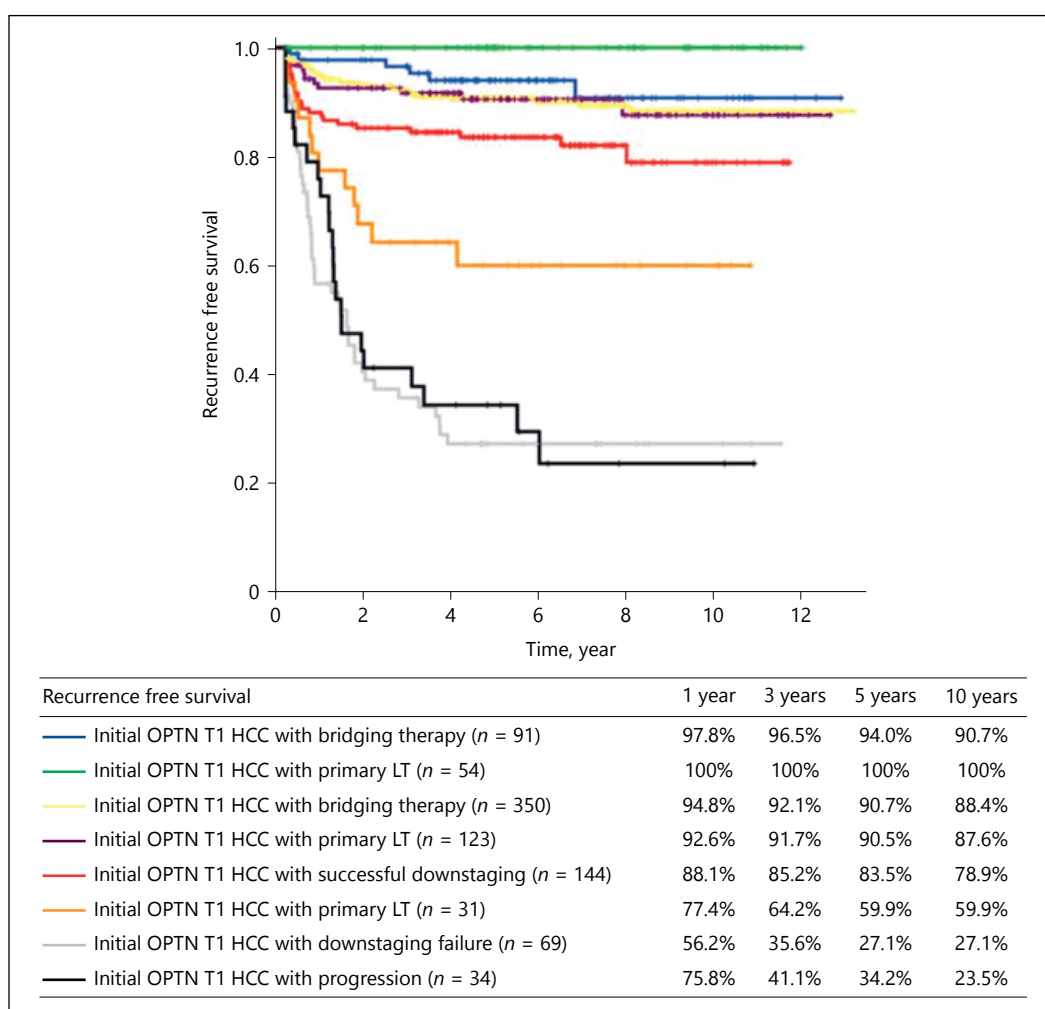


Fig. 1. (for Abstract no P-034).

0.001 and HR, 2.42, $P < 0.001$) were independent predictors for worse RFS and OS. **Conclusion:** The impact of bridging therapy on survival outcomes is limited in patients with early staged HCC, whereas acceptable long term outcomes can be achieved after successful downstaging in patients with OPTN T3 HCC.

P-035

Assessment of Recurrence Factor for Treated Hepatocellular Carcinoma by Using Intraoperative Radiofrequency Ablation

Hyuk Soo Eun^{1,2}, Sang Ok Jung¹, Min Ji Cho¹, Woo Sun Rou^{1,2}, Seok Hyun Kim^{1,2}, Byung Seok Lee^{1,2}

¹Department of Internal Medicine, Chungnam National University Hospital, 282, Munwha-ro, Jung-gu, Daejeon, 34952, Republic of Korea, Korea, ²Department of Internal Medicine, School of Medicine, Chungnam National University, 266, Munwha-ro, Jung-gu, Daejeon, 35015, Republic of Korea, Korea

Background/Aims: Despite the highly complete tumor necrosis rate of radiofrequency ablation (RFA), tumor recurrence, either locoregional or newly developing lesion, was regarded as significant issue. Recurrence reduction through appropriate procedure selection as well as patients selection could improve survival of patients. Therefore, we analyzed the conditional factor for recurrence after intra-operative RFA treatment on hepatocellular carcinoma (HCC). **Methods:** We investigated 98 patients who were treated with intra-operative RFA as initial treatment for HCC. The mean follow-up period was 33 ± 14.5 months. We evaluated the disease-free survival of recurred patients, including local tumor progression (LTP) and intrahepatic distant recurrence (IDR). For these patients, multiple factors were assessed to their significance for recurrence and survival. **Results:** Almost baseline characteristics were not shown statistically significant difference. Incidence of overall recurrence was 47.9 %. LTP was found in 20 of 47 patients (20.4 %) and occurred 4 - 33 months [median period: 14 months] after RFA. IDR was found in 27 of 47 patients (27.5 %) and occurred 6 - 88 months [median period: 22 months] after RFA. Interestingly, on multivariate analysis, serum alpha-fetoprotein (AFP) was significantly associated factor with tumor recurrence [$p = 0.006$, 95% C.I.: 1.001–1.007, HR = 1.004]. In addition, INR and Child-Pugh scores, factors representing severity of underlying liver disease status, were significantly associated with survival of the patients ($p = 0.039$ and $p = 0.046$). Especially, AFP was also significantly associated factor with survival of the patients [$p = 0.016$, 95% C.I.: 1.001–1.006, HR = 1.004]. After subgroup analysis for recurred patients, we found that patients with higher AFP levels had more recurrence patterns of LTP rather than IDR. **Conclusion:** Patients with high AFP level received intraoperative RFA for

HCC should be carefully followed-up and considered more active radical treatment modality because of higher risk of recurrence and mortality.

P-036

Albumin Bilirubin (ALBI) Score as a Predictive Value of Post Hepatectomy Liver Failure Comparable to ICG R15 in HCC

Hyun Joon Park¹, Sung Jun Kim¹, Joon Ho Jeong¹, Kwang Il Seo¹, Sang Uk Lee¹, Byung Cheol Yun¹, Byung Hoon Han¹, Dong Hoon Shin¹, Young Il Choi¹, Hyung Hwan Moon¹

¹Kosin University College of Medicine, Korea

Aims: Indocyanine Green (ICG) R15 test has been used for predicting hepatic dysfunction after liver resection. Recently, albumin bilirubin (ALBI) score has been proposed evaluating hepatic dysfunction. We aimed to investigate whether albumin-bilirubin (ALBI) score could be used as predictor of postoperative hepatic dysfunction in patients with hepatocellular carcinoma (HCC). **Methods:** We reviewed medical records of HCC patients underwent surgical resection after ICG15 test in Kosin University Gospel Hospital from January 2014 to November 2018. Clinical characteristics, laboratory findings, outcomes of post hepatectomy liver failure (PHLF) and ICG score were collected. We compared ICG score and ALBI score between non-PHLF group and PHLF group. **Results:** 105 HCC patients received surgical resection after ICG test. The mean ($\pm$ SD) of age of study patients were $61.0 (\pm 8.88)$ years. Fifty-nine (56.2%) patients were treated with major resection. PHLF developed in 74 patients (70.5%). PHLF grade A, grade B, grade C were 6 (8.1%) patients, 63 (85.1%) patients and 5 (6.8%) patients, respectively. In multi-variable analysis, ICG R15 (OR 0.94 [95% CI: 0.88–0.99]) and ALBI score (OR 0.40 [95% CI: 0.16–0.95]) were significant values predicting development of PHLF. ALBI scores of PHLF group (-2.37 ± 0.59) were significantly lower than those of non-PHLF group (-2.67 ± 0.42) ($P = 0.014$). ICG scores of PHLF group (15.52 ± 11.60) were also significantly higher than those of PHLF group (10.29 ± 7.42) ($P = 0.022$). The AUC values of the ALBI score and ICG score for predicting PHLF were 0.614 and 0.649, respectively. **Conclusions:** The ALBI score could assess hepatic dysfunction after liver resection in HCC patients as ICG R15. Therefore, the ALBI score could be an alternative predictor of PHLF development in HCC patients.

P-037

Prognosis of Patients with Advanced Hepatocellular Carcinoma Underwent by Surgical Resection After Sorafenib Resistance (Report of 14 Cases)

Liqun Wu^{1,2}, Jingyu Cao^{1,3}, Zixiang Li^{1,4}, Zusen Wang^{1,3}, Bing Han^{1,3}, Wei Rao^{1,2}, Yunjin Zang^{1,2}

¹The Affiliated Hospital of Qingdao University, China, ²Liver Disease Center, China, ³Department of Hepatobiliary & Pancreatic Surgery, China, ⁴Department of Interventional medicine, China

Objective: This article retrospectively analyzed the prognosis of patients with advance of HCC after sorafenib resistance in the Affiliated Hospital of Qingdao University, and explored the prognosis and possible influencing factors. **Methods:** From October 2008 to February 2017, a total of 170 patients with advanced HCC were taking sorafenib for more than 3 months. There were 14 patients (8.2%) underwent surgical resection after sorafenib resistance. The follow-up time was up to March 2019 or the patients died, the median follow-up time after taking sorafenib was 33.8 months (24.4–94.2 months). **Results:** There were 9 patients with solitary tumor, and the other 5 patients in the liver and abdominal cavity, The surgical methods included 7 cases of hepatectomy, 4 cases of abdominal tumor resection, 2 cases of hepatectomy and abdominal tumor resection, and 1 case of partial lung lobectomy. The postoperative complication rate was 14.3%. Pathological results showed the HCC in 11 patients, the necrosis and granulation tissue in 3 patients. The treatment models after resection included oral regorafenib (n = 5), everolimus (n = 2, by NGS), continuing sorafenib (n = 4), and others (n = 3). By the end of follow-up, HCC progression occurred in 10 patients after surgical resection, and the median time to progression time (rTTP) was 7.7 months (95% CI: 5.1–10.3 months); and the median overall survival time (mOS) was 11.8 months (95% CI: 8.3–15.3 months) after surgical resection, and 5 patients survived to date. The mOS time from sorafenib to now was 57.9 months (95% CI: 26.9–88.9 months). **Conclusion:** Surgical resection is an effective treatment for the patients taking sorafenib while sorafenib resistance. After resection, the treatment model should be changed sorafenib to the second-line targeted drugs (regorafenib) or other drugs on the basis of the second-generation gene sequencing (NGS) results.

P-038

A Case of Primary Hepatic Mucosa-Associated Lymphoid Tissue Lymphoma Developed from the Normal Liver

Takeshi Aiyama¹, Ryoji Yokoyama¹, Saori Sugii¹, Koichiro Sarashina³, Hiroko Gotoda², Nobuhiko Abe³, Shiro Nakano¹

¹Department of Surgery, Abashiri-Kosei General Hospital, Japan, ²Department of Surgical Pathology, Sapporo-Kosei general Hospital, Japan, ³Department of Internal Medicine and Gastroenterology, Abashiri-Kosei Hospital, Japan

Introduction: Primary hepatic mucosa-associated lymphoid tissue (MALT) lymphoma is a very rare disease and thus there is no consensus on the best approach to its management. Here, we report a new case of MALT lymphoma without chronic liver disease or autoimmune disease that was successfully resected with a partial hepatectomy. **Case Report:** A 55-year-old man who had no medical history was diagnosed with a liver tumor (41 mm in segment 4) by abdominal ultrasonography at a routine medical examination. Both his HBs antigens and HCV antibodies were negative, and tumor markers such as alpha-fetoprotein, the protein induced by vitamin K absence and soluble interleukin-2 receptors, were also negative. All the enzymes of the hepatic-cystic system were within the normal range. Contrast-enhanced computed tomography (CT) imaging revealed the hepatic mass as a faint enhancement during the arterial phase, and from the iso- to the slightly lower enhancement in the portal and delayed phase. Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging (MRI) showed low on the T1-weighted images, moderate on the T2-weighted images and high intensity on the diffusion-weighted images of the mass in the liver. The infiltrative pattern of the lesions was seen both in CT and MRI, with no distortion of the vessels traversing the mass. Whole-body positron emission tomography CT showed a high accumulation of fluorodeoxyglucose in the hepatic mass; however there was no abnormal uptake in other organs. A biopsy of the liver tumor was performed, and MALT lymphoma was strongly suspected. The patient underwent a partial hepatectomy. The histopathologic analysis confirmed the diagnosis: hepatic MALT lymphoma positive for CD 20, CD79a, bcl-2 and PAX5, and negative for cyclin D1. The patient has been disease-free for six months postsurgery. **Conclusion:** Primary hepatic MALT lymphoma can occur in the normal liver, and surgical treatment may be the best choice.

P-039

Long Term Survival After Multiple Resections and Radiofrequency Ablation for Metachronous Development of Hepatocellular Carcinoma Following Intrahepatic Cholangiocarcinoma in a Single Patient

Masahiro Hagiwara¹, Yoshinari Saitou¹,
Hiroyuki Takahashi¹, Kouji Imai¹, Hideki Yokoo¹,
Naoto Matsuno¹, Yasuo Sumi¹, Hiroyuki Furukawa¹

¹Asahikawa Medical University, Japan

A 53-year-old man was diagnosed as primary liver tumor with 2.3 cm in size in the segment V following detailed investigation for elevated liver enzymes. He underwent partial hepatectomy and the histological diagnosis revealed intrahepatic cholangiocarcinoma (ICC). 6 years and 8 months later, the patient was found to have another liver tumor with 2.0 cm in the segment I. He underwent partial hepatectomy and the histological diagnosis revealed moderately differentiated hepatocellular carcinoma (HCC). After that, He developed 2.1 cm of liver tumor in segment V 10 years and 1 month after first surgery, 2.7 cm of liver tumor in the segment VII 16 years and 3 months after first surgery, and 1.1 cm of liver tumor in the segment VIII 18 years and 1 month after first surgery. He underwent partial resection in the first two occasions and radiofrequency ablation (RFA) in the last occasion. The histological diagnosis showed well-differentiated, moderate to well-differentiated, and well-differentiated HCC respectively. Eventually, the patient underwent four times of hepatectomy and one time of RFA for metachronous development of ICC and HCC. The patient is alive and well without recurrence 18 years and 6 months after the first surgery and 2 years and 3 months after the last surgery.

P-040

Asymptomatic Late Hepatic Artery Thrombosis After Living Donor Liver Transplantation: A Case Report

Thanh V. Le¹, Quang V. Vu¹, Linh V. Ho¹, Hieu T. Le¹,
Loi V. Le¹, Luc T. Dao¹

¹Military Central Hospital 108, Vietnam

Objective: Late hepatic artery thrombosis (HAT) is a rare complication after orthotopic liver transplantation and generally associated with a milder clinical course than acute HAT. We report an asymptomatic late hepatic artery thrombosis after living donor liver transplantation. The patient was well recovered without retransplant. **Description:** The recipient was a 59 years old male with the right lobe graft. Postoperative day 58, after successfully treating of CMV infection, he had abnormal liver enzymes tests, without any



Fig. 1. (for Abstract no P-040).

clinical symptom. CT scanner showed no specific changes of the graft, we suspected acute rejection, therefore liver biopsy and steroid pulse therapy were applied; liver biopsy results found no rejection and the level of serum liver enzymes were still high. Angiogram showed hepatic artery thrombosis at the anastomose site, but there were some collateral. Because there was no donor for retransplant, close observations and prophylactic treatments were conducted. Four months after liver transplantation there was no biliary complication. **Discussion:** HAT is usually associated with CMV infection. Angiography is better than CT in diagnose HAT and confirm if collateral is available. Collateral was the good prognosis factor even though it was not enough. Prophylactic treatments and close observations including blood test and CT scanner are very useful. Retransplant should be considered but not always available. **Conclusions:** Late HAT with good collateral could be recovered without retransplant. Digital Subtraction Angiography is useful to detect those collateral.

P-041

A Combined Resection of Vena Cava and Associated Reconstruction Using Cryo-Preserved Venous Allograft in Hepatic Resection for Intrahepatic Cholangiocarcinoma

Junichi Arita¹, Junko Hiroyoshi¹, Akihiko Ichida¹, Takeaki Ishizawa¹, Nobuhisa Akamatsu¹, Junichi Kaneko¹, Kiyoshi Hasegawa¹

¹The University of Tokyo, Japan

Background/Aim: The best choice of a graft in venous reconstruction accompanied with hepatic resection is debatable. **Methods:** A 66-year old woman presented with an intrahepatic cholangiocarcinoma sizing 8 cm in diameter at another hospital. As decided as unresectable, a total of 14 cycles of GC chemotherapy was performed. She was referred to our hospital, and extend right hepatectomy with venous reconstruction was planned despite invasion to IVC, RHV, MHV, and a part of circumference of LHV. **Results:** After laparotomy and mobilization of the liver, intraoperative ultrasound revealed that 1/3 of IVC circumference, a major part of MHV, a small part of circumference of LHV were invaded, which lead to decision as resectable. RHA and right branch of portal vein were ligated and cut, and hepatic parenchymal transection toward the left side of the trunk of MHV was completed. The specimen was connected only with IVC and LHV at this point of time, and subsequent incise of these veins were performed under hepatic inflow occlusion, cross-clamp of IVC, and cross-clamp of LHV, making the specimen taken out. A cryo-preserved IVC allograft, prepared along with hepatic parenchymal transection on the back-table, was used as a patch on defect of IVC and MHV. Just completing reconstruction, intraoperative ultrasound revealed fair intrahepatic venous flow. Operating duration was 8 hours and 21 minutes, and 1140 mL of blood loss was estimated. Postoperative course was fair with Clavien-Dindo grade 2A of pleural effusion, and she was discharged from hospital on the 7 post-operative day. After 4 months, she is fair without signs of tumor recurrence. **Conclusion:** A use of cryo-preserved venous allograft is a choice in venous reconstruction in hepatic resection, because it does not require additional incision or surgical procedure and provides a choice among various sized and shape.

P-042

A Resected Case of Fibrolamellar Hepatocellular Carcinoma Which Recurred 2 Years After the Primary Operation

Kyung Hwa Park¹, Taku Aoki¹, Takashi Arakawa¹, Takayuki Shimizu¹, Kazuma Tago¹, Nobuhiro Harada¹, Takatsugu Matsumoto¹, Yuki Sakuraoaka¹, Takayuki Shiraki¹, Shozo Mori¹, Yukihiro Iso¹, Keiichi Kubota¹

¹Department of Gastroenterological Surgery, Dokkyo Medical University, Tochigi, Japan

Case Presentation: A 21-year-old man was admitted to our hospital for the treatment of a liver tumor which was found due to abdominal discomfort. Liver functional tests were all normal and hepatitis virus markers were all negative. Serum AFP level was within a normal range, while the plasma PIVKA-II level was slightly elevated. Abdominal CT showed a tumor, 8.5 cm in diameter, located in segments 4 and 8 of the liver. The central portion of the tumor was predominantly enhanced in the arterial phase and prolonged enhancement was observed in the venous phase. A large calcification was seen inside of the tumor. EOB-MRI showed low intensity in the central part of the tumor while relatively high intensity in the peripheral part of the tumor. FDG-PET CT showed slightly increased FDG uptake in the tumor. A fibrolamellar carcinoma (FLC) was suspected and central bisegmentectomy of the liver was performed. Pathological examination of the resected specimen confirmed the presence of FLC. Two years after the primary resection, tumor recurrence was found in the liver (S6) and regional lymph nodes by CT. Partial hepatectomy and lymphadenectomy was performed and pathological examination confirmed the recurrence of FLC. **Discussion:** FLC is very rare entity of hepatocellular carcinoma, and it has been reported that FLC follows a relatively favorable clinical course. However, our case presented an aggressive course with both intra- and extra-hepatic early recurrence. This case is particular rare, and herein is reported with literature review.

Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy

P-043

Efficacy and Safety of Percutaneous Radiofrequency Ablation in Treatment of Small Hepatocellular Carcinoma in Myanmar (Single Centre Study)

A Mi Mi Kyaw¹, Khaing Zar Tun²,
Naomi Khaing Than Hlaing¹

¹Department of Hepatology, Mandalay General Hospital, Myanmar, ²Department of Radiology, Mandalay General Hospital, Myanmar

Background: Hepatocellular Carcinoma (HCC) is the 2nd most important cause of cancer death globally. Radiofrequency Ablation (RFA) is the most commonly used local ablation therapy for small HCC because the technique is highly effective, minimally invasive and requires fewer sessions. Aim of this study was to evaluate the safety and efficacy of Percutaneous RFA in patients with small HCC. **Materials and Methods:** Patients diagnosed with HCC who were suitable for local ablation (Percutaneous RFA) were retrospectively analyzed at Department of Hepatology, Mandalay General Hospital from April 2018 to March 2019. Inclusion criteria; HCC patients with a single tumor ≤ 5 cm and Child Pugh A or B-7. Tumor location is near to diaphragm, vital organs, major vessels, bile duct and Liver capsule were excluded. RF electrode Type; STARmed gauge (17), length 15 cm adjustable electrode. One month after ablation, tumor response was assessed with contrast enhanced Liver four phases CT scan. **Results:** A total of 39 HCC patients were treated with RFA. The

baseline characteristics are mean age 60.6 ± 8.3 (33–76), Sex; Male 49% & Female 51%, Liver Cirrhosis grade; Child A 56% and Child B-7 44%, etiology of HCC; HBV 50%, HCV 40%, HBV & HCV Co infection 5% and Non B Non C 5%. There was no serious adverse events (bowel perforation, internal bleeding, haemothorax and sepsis) except slight abdominal discomfort. According to mRECIST criteria, complete response was seen in 74% and partial response in 26% of the patients. **Conclusion:** This study demonstrated that; Although RFA was safe and effective for early HCC, a significant portion needs to be treated with repeated RFA or combination therapy.

P-044

Second Line Treatment for Recurrent Hepatocellular Carcinoma after Curative Treatment -Single Center Experience-

Soung Won Jeong¹, Jae Young Jang¹, Tom Ryu¹,
Young Chang¹, Jeong-Ju Yoo², Sae Hwan Lee³,
Sang Gyune Kim², Sang-Woo Cha¹, Young Seok Kim²,
Young Deok Cho¹, Hong Soo Kim³

¹Soonchunhyang University Seoul Hospital, Korea,

²Soonchunhyang University Bucheon Hospital, Korea,

³Soonchunhyang University Cheonan Hospital, Korea

Background/Aim: We investigated the recurrence of hepatocellular carcinoma (HCC) after curative treatment and determined the efficacy of second line treatment. **Methods:** This study included 230 patients who had been diagnosed with HCC and had curative treatment such as radiofrequency ablation (RFA), surgery or liver transplantation. Data on recurrence, survival, and second line treatment after curative treatment were collected and analyzed. Recurrence rates were compared with the chi-square test, and cumulative survival rates were compared with log-rank and Kaplan-Meier test. P-values < 0.05 were considered statistically significant. **Result:** Average follow up duration was 46.37 months (1–180 months). The total recurrence rate after curative treatment for HCC was 41.3%. The recurrence rates after surgery including liver transplantation and RFA were 43.4% and 38.6%, respectively. There was no significant difference in recurrence rate after surgery or RFA ($P = 0.463$). However, the cumulative survival rate after surgery including liver transplantation was significantly higher than that after RFA ($P = 0.032$). Transarterial chemoembolization (TACE) was performed in 50 of 95 patients (52.6%), as second line treatment. Other patients received local treatment (RFA or CyberKnife) (17.9%), sorafenib (14.7%), or other treatments (14.8%) as second line treatment. Surgery was performed in 1 patient with recurrent HCC after RFA. The 5-year survival rate in patients with recurrent HCC was 64.1%. The survival rate was not significantly different between patient treated with TACE and non-TACE as second line treatment ($P = 0.760$) (Figure). **Conclusion:** Although recurrence rates after surgery

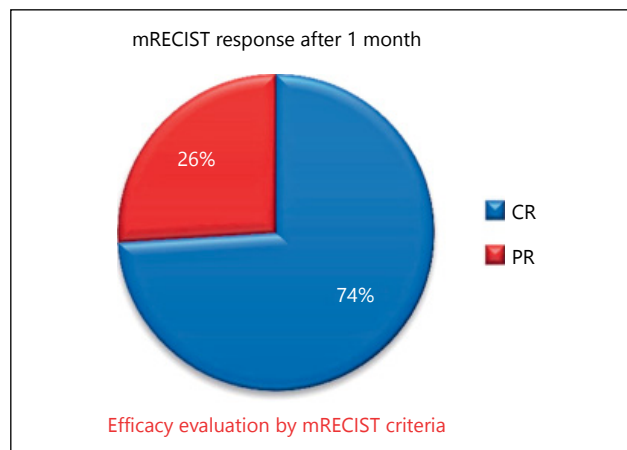


Fig. 1. (for Abstract no P-043).

and RFA were not significantly different, the cumulative survival rate was significantly different between the 2 groups. TACE was the most common second line treatment, but the cumulative survival rate was not significantly different between patients treated with TACE and non-TACE as second line treatment.

P-045

Radiofrequency Ablation versus Surgical Resection for the Treatment of Solitary Hepatocellular Carcinoma 2 cm or smaller: A 10-Year experience of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation in Taiwan

Ching-Sheng Hsu¹, Chao-Chuan Wu², Kuo-Chih Tseng³, Kuo-Chih Tseng³

¹Liver Diseases Research Center, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan, ²Department of Surgery, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan, ³Division of Gastroenterology, Department of Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan

Background: Radiofrequency ablation (RFA) has been increasingly utilized for treatment of hepatocellular carcinoma (HCC) measuring 2 cm or smaller. Long-term results of RFA, especially in comparison to surgical resection, remain controversial. We aimed to evaluate the long-term outcomes of patients who underwent surgical resection or RFA for HCC. **Methods:** 194 patients with HCC who underwent surgical resection or and 82 received RFA during a 10-year period were consecutively enrolled in Taipei Tzu Chi Hospital. Patients' characteristics, overall (OS), recurrence-free (RFS), and tumor-free survival (TFS) were compared between the two groups and in subgroup analyses. **Results:** The 1-year, 2-year, 3-year, 4-year OS were significantly higher in the surgical resection group compared with the RFA group, while the 5-year and 10-year OS were comparable between two groups. Compared to the RFA group, the surgical resection group had significantly higher 1-yr, 2-yr RFS, but comparable 10-yr RFS. The 1-year, 2-year, 3-year, 4-year, 5-year TFS were significantly higher in the surgical resection group compared with the RFA group, while there was no significant difference in the 10-year TFS between two groups. Nonetheless, subgroup analyses showed that the surgical resection group had a significantly higher 10-year OS than the RFA group in patients with BCLC stage A. In multivariate analysis, Child-Pugh score was the only significant predicting factor for all survival analyses. **Conclusions:** Although surgical resection provides a better short-term survival than RFA, the liver reserve is the main predictor of long-term survival in patients with HCC receiving resection or RFA treatments.

P-046

Current Status of Therapeutic Choice and Feasibility for Hepatocellular Carcinoma Patients Over 70 Years Old

Hyun Woong Lee¹, Seoung Yoon Rho¹, Kyung Sik Kim¹, Do Young Kim¹

¹Yonsei University College of Medicine, Korea

Aims: We investigated how the detailed treatment of hepatocellular carcinoma in elderly patients and overall survival of each treatment modalities. **Method and Materials:** From January 2003 to December 2005 and January 2008 to December 2014, the National Cancer Center (NCC) and Korean Liver Cancer Study group (KLCSG) collected 3,006 clinical datas from HCC patients over 70 years old investigating Korea Central Cancer Registry (KCCR) records at 54 medical centers in south Korea. Using this data we analyzed current treatment modality and overall survival of each modalities in treating HCC patients over 70 years old. **Results:** In Period 2003–2005, there were 578 patients and in period 2008–2014, 2428 patients were analyzed. Transarterial therapy (period 2003–2005: 49.1%, period 2008–2014: 44.4%) was the most commonly used treatment modality. Among them, Transarterial chemoembolization (TACE) with gelatin sponge occupied largest proportion (96.1%, 65.6%). In overall survival analysis, surgical resection showed statically significant superiority than other treatment modalities ($P < 0.001$), followed by local ablation therapy and Transarterial therapy in both periods. However, there were no statistically significant differences in propensity score matching for surgical resection, local ablation therapy, and transarterial therapy for relatively early stage lesions. In subgroup analysis, there was statistically significant difference between the surgical resection, local ablation therapy, transarterial therapy and the rest of other treatment modalities in the 70–75 year period. However, there was no significant difference between surgical resection, local ablation therapy, transarterial therapy in the ages of 75–80 years and over 80 years. **Conclusion:** Transarterial therapy was the most commonly used treatment modality in HCC patients over 70 years old, and surgical resection did not show statistically significant superior overall survival rate than Transarterial therapy.

P-047

BCLC-B Subclassifications Associate with Tumor Response and Liver Decompensation to Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma

Chen-Ta Chi¹, I-Cheng Lee¹, Rheun-Chuan Lee²,
Chien-Wei Su¹, Ming-Chih Hou¹, Yee Chao³,
Yi-Hsiang Huang^{1,4}

¹Division of Gastroenterology and Hepatology, Department of Medicine, Taiwan, ²Department of Radiology, Taipei Veterans General Hospital, Taiwan, ³Cancer Center, Taipei Veterans General Hospital, Taiwan, ⁴Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taiwan

Background/Aim: Transarterial chemoembolization (TACE) is the standard of care for intermediate stage hepatocellular carcinoma (HCC). But heterogeneity in tumor and clinical characters result in varied responses to TACE. The study aimed to assess BCLC-B subclassifications in relating to liver decompensation and tumor response in patients treated with TACE. **Methods:** From October 2007 to January 2017, consecutive 531 BCLC-B HCC patients undergoing TACE in Taipei Veterans General Hospital were retrospectively reviewed. Objective response rate (ORR) was evaluated by RECIST 1.1 and the incidence of liver decompensation among BCLC-B subclassifications (Bolondi's, Kinki, and up-to-11 criteria) were evaluated. Factors association with ORR and liver decompensation were analyzed. **Results:** The ORRs were 51.2%, 38.5%, 16.7%, and 23.5% in Bolondi's subclassification B1, B2, B3, and B4, respectively ($p < 0.001$); 50.6%, 36.9%, and 23.5% in Kinki criteria B1, B2, and B3, respectively ($p = 0.005$); 50.2%, 26.6%, and 13.6% in up-to-11 subclassification B1, B2, and B3, respectively ($p < 0.001$). Age, AST, AFP, and the three BCLC subclassifications were factors associated with ORR. The incidences of liver decompensation in acute stage were 18.3%, 19.7%, 52.8%, and 76.5% in Bolondi's B1, B2, B3, and B4, respectively ($p < 0.001$); 20.5%, 22.1%, and 76.5% in Kinki criteria B1, B2, and B3, respectively ($p < 0.001$); 16.6%, 32.6%, and 45.5% in up-to-11 subclassification B1, B2, and B3, respectively ($p < 0.001$). ALT >40 IU/L, AST >45 IU/L, ALBI II/III, the three BCLC subclassifications, unilobar location, and AFP >200 ng/mL were predictors of post-TACE liver decompensation. In addition, the incidence of chronic liver decompensation and ALBI grade migration were also associated with BCLC-B subclassification. **Conclusions:** Not all BCLC B patients are eligible for TACE. The net benefit of TACE should be judged according to BCLC B subclassifications.

P-048

Clinical Outcomes of Stereotactic Body Radiation Therapy for Single Viable Hepatocellular Carcinoma at the Site of Incomplete Transarterial Chemoembolization

Jinhong Jung¹, Hee Hyun Park¹, So Yeon Kim²,
Young-Suk Lim³, Han Chu Lee³, Jin-hong Park¹,
Jong Hoon Kim¹, Sang Min Yoon¹

¹Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea, ²Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Korea, ³Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Korea

Background/Aim: Transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) patients may show unsatisfactory local control, with incomplete TACE cases having viable HCCs after multiple consecutive TACE. Moreover, no study to date has provided clear recommendation on effective local treatment option for residual viable HCC at the site of incomplete TACE. Therefore, we evaluated the clinical outcomes of patients who received stereotactic body radiation therapy (SBRT) for single viable HCC at incomplete TACE sites. **Methods:** A total of 302 patients were treated with SBRT for single viable HCC after incomplete TACE between March 2012 and July 2017 at Asan Medical Center. Incomplete TACE was defined as evidence of viable HCC at the site of TACE on follow-up images following one or more consecutive TACE procedures. **Results:** The median follow-up period was 32.9 months (interquartile range [IQR], 23.6–41.7) and the median tumor size was 2.0 cm (IQR, 1.5–2.5). Almost all patients had ECOG performance status of 0 (93.0%). The median radiation dose was 45 Gy (36–60) with a median fraction size of 15 Gy (12–20). The local control rate at 3 years was 91.2%. The overall survival, out-of-field intrahepatic recurrence-free survival, and distant metastasis-free survival rates at 3 years were 72.7%, 40.4%, and 82.5%, respectively. Elevations in the level of transaminases or bilirubin of CTCAE grade ≥ 2 , which may be related to SBRT without progression of intrahepatic HCC, were observed in 8 patients (2.6%). Worsening of Child-Pugh score ≥ 2 was observed in 5 patients (1.7%). No patients experienced late gastroduodenal bleeding within the radiation field. **Conclusion:** SBRT showed excellent clinical outcomes in terms of local control, survival, and adverse events when used as an ablative treatment modality for residual single viable HCC at the site of incomplete TACE.

P-049**A New Prognosis Prediction Model in Patients with Hepatocellular Carcinoma after Yttrium-90 Radioembolization**

Jae Seung Lee¹, David Soaik Kim¹, Han Ah Lee²,
Mi Young Jeon¹, Beom Kyung Kim¹, Jun Yong Park¹,
Do Young Kim¹, Sang Hoon Ahn¹, Soon Ho Um²,
Kwang-Hyub Han¹, Yeon Seok Seo², Seung Up Kim¹

¹Yonsei University College of Medicine, Korea, ²Korea University College of Medicine, Korea

Background and Aims: Few studies reported the treatment outcomes of trans-arterial radioembolization (TARE) using Yttrium-90 (90Y) for hepatocellular carcinoma (HCC). We established and validated a new prognosis prediction model for patients with HCC treated with TARE. **Methods:** Between 2010 and 2017, 113 and 35 patients with intrahepatic HCC treated with TARE were selected for training and validation cohorts, respectively. The modified RECIST (mRECIST) criteria were used for response evaluation at 1, 3 and 6 months after TARE. **Results:** In the training cohort, the median age was 64.1 years (92 male and 19 female) and the median survival after TARE was 50.3 months. Using five variables including low serum albumin (<3.5 g/dL; hazard ratio [HR]= 5.446), high alpha-fetoprotein (AFP, 200 ng/mL; HR = 5.071), tumors above three (HR = 2.933), portal vein thrombosis (HR = 4.915) and hepatic vein invasion (HR = 8.500), and two on-treatment variables including no des-gamma-carboxy prothrombin response (HR = 15.346) and progressive disease

at 3 months after TARE (HR = 4.154) which were independently associated with mortality (all $P < 0.05$). A new prediction model for TARE (Y-scoring system) was established from the training cohort. The predictive accuracy of Y-scoring system to predict 6 (area under curve [AUC]=0.845), 9 (AUC = 0.868), and 12 months mortality (AUC = 0.886) after TARE was acceptable (all $P < 0.05$). In the validation cohort, the predictive accuracy of Y-scoring system was similarly maintained (AUC 0.737–0.901 at 6 to 12 months). **Conclusions:** Our new predictive model might be useful to stratify different prognosis for patients with HCC treated with TARE. Further validation from a large cohort is required.

P-050**Platelet-to-Lymphocyte Ratio Prior to Transarterial Radioembolization for Hepatocellular Carcinoma is More Predictive of Disease Response than Neutrophil-to-Lymphocyte Ratio**

Kliment K. Bozhilov¹, Sandi Kwee², Linda Wong^{1,2}

¹University of Hawaii, USA, ²Queen's Medical Center, USA

Background/Aim: Inflammation-based scores, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been used as prognostic values for hepatocellular carcinoma (HCC). However, there is

Table 1. (for Abstract no P-049)

Risk factors	Univariate P value	Multivariate analysis		Scoring
		P value	Hazard ratio (95% CI)	
Serum albumin <3.5 g/dL	<0.001	0.001	5.446 (2.004–14.798)	2
Alpha-fetoprotein in, baseline >200 ng/mL	0.026	0.001	5.071 (1.949–13.196)	2
Three or more tumors	0.012	0.029	2.933 (1.116–7.706)	1
First order branch portal vein thrombosis	0.008	0.032	4.915 (1.147–21.066)	2
Hepatic vein invasion	0.014	0.003	8.500 (2.051–35.226)	3
No DCP response at 3 months	<0.001	<0.001	15.346 (4.424–53.235)	5
Progression by mRECIST criteria at 3 months	0.004	0.008	4.154 (1.453–11.872)	1

Cohorts	Time points after TARE	Total patients	Mortality	AUC (95% II)	P value
Training	at 6 months	113	9 (8.0)	0.845 (0.684–1.000)	0.002
	at 9 months	102	12 (11.8)	0.868 (0.728–1.000)	0.001
	at 12 months	92	17 (18.5)	0.886 (0.797–0.975)	<0.001
Validation	at 6 months	35	11 (31.4)	0.901 (0.767–1.000)	0.005
	at 9 months	32	15 (46.9)	0.818 (0.609–1.000)	0.017
	at 12 months	32	18 (56.2)	0.737 (0.516–0.958)	0.074

CI, confidence interval; AUC, area under the ROC curve.

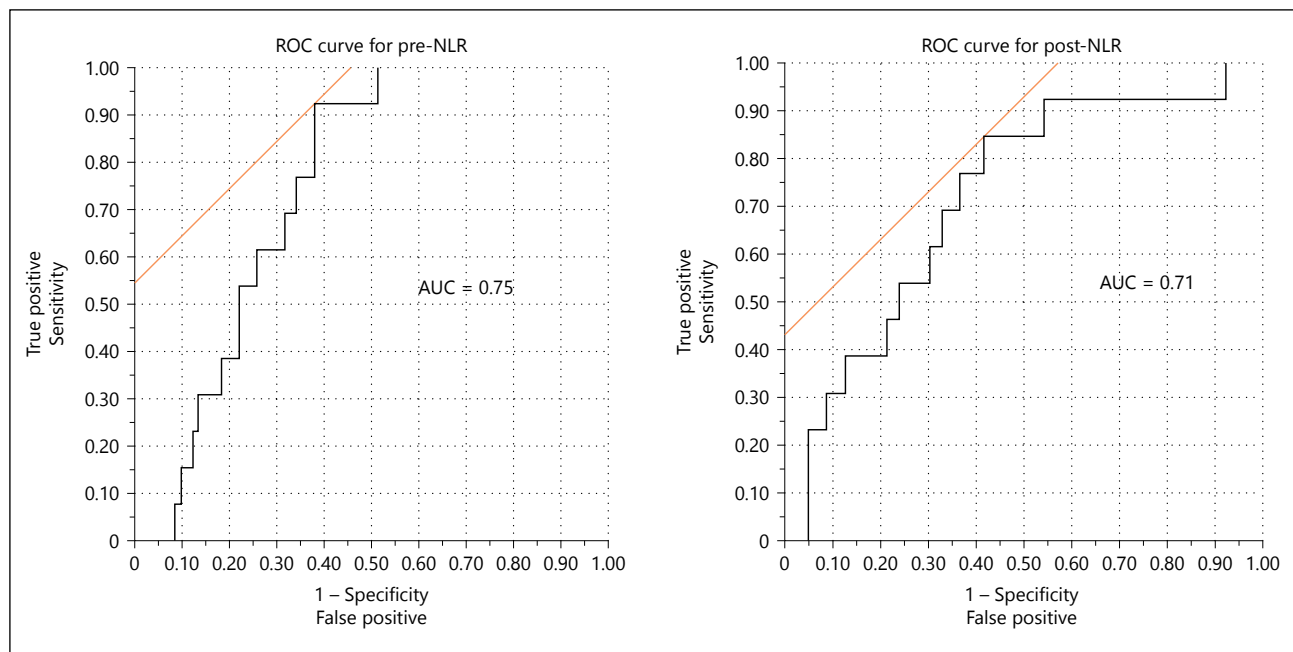


Fig. 1. (for Abstract no P-050).

a paucity of data on the predictive value of these serum biomarkers on response to transarterial radioembolization (TARE) using Yttrium90 (Y90) microspheres for HCC. **Methods:** We performed a single-institution retrospective review of HCC patients undergoing TARE as primary treatment between 1994 to 2018. Laboratory tests and imaging at the time of initial treatment and at 3-month follow-up were used to measure patient demographics, NLR, PLR, tumor number, size, and response using the modified response criteria in solid tumors (mRECIST). The area under the receiver operator curves (AUROC) values were used to predict partial and complete response. **Results:** Complete laboratory and imaging data was available for 87 of the 110 patients with HCC who underwent TARE. At three-month follow-up, as measured by mRECIST, 63 (72%) patients had stable disease, 10 (12%) had progressive disease, 4 (4.6%) had complete response, and 10 (12%) had partial response. A paired students t-test demonstrates a difference between NLR in pre- and post-TARE (3.29 vs. 8.08, $p < 0.001$) and in PLR pre- and post-TARE (9.00 vs. 19.83, $p < 0.001$). AUROC analysis identified PLR pre-TARE and post-TARE as the best predictors of partial and complete response with area under the curve (AUC) values of 0.75 and 0.71, respectively. Pre and post-NLR and changes in PLR and NLR were poor predictors of clinical response with AUC values levels < 0.65 . **Conclusion:** PLR values may have more prognostic value than NLR for predicting early response to Y90-TARE in HCC. Future studies could potentially identify a cohort of patients that are more likely to respond to Y90-TARE for HCC.

P-051

Prognostic Significance of Apparent Diffusion Coefficient in Hepatocellular Carcinoma Patients treated with Stereotactic Ablative Radiotherapy

Wen-Yen Huang¹, Cheng-Hsiang Lo¹, Wei-Chou Chang²

¹Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taiwan, ²Department of Radiology, Tri-Service General Hospital, National Defense Medical Center, Taiwan

Aim: To evaluate the prognostic performance of diffusion-weighted magnetic resonance imaging (DW MRI) in patients with hepatocellular carcinoma (HCC) treated with stereotactic body radiotherapy (SBRT). **Methods:** This retrospective study included HCC patients treated with SBRT who had DW MRI data at baseline and within 6 months post-SBRT. The apparent diffusion coefficients (ADCs) of all lesions were determined. In-field control (IFC) was assessed for each tumor according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). **Results:** Thirty-four patients with 45 lesions were analyzed. On the first post-SBRT MRI, 13 lesions (28.9%) had a complete response (CR), 12 (26.7%) had a partial response (PR), 17 (37.8%) had stable disease (SD), and 3 (6.7%) had progressive disease. On subsequent imaging, 4 lesions with PR were upgraded to CR, and 9 that were SD were reclassified as CR or PR; hence, the response rate improved from 55.6% to 75.6%. The pre- and post-SBRT ADCs (mean $\pm$ standard deviation) were 1.43 ± 0.28 and

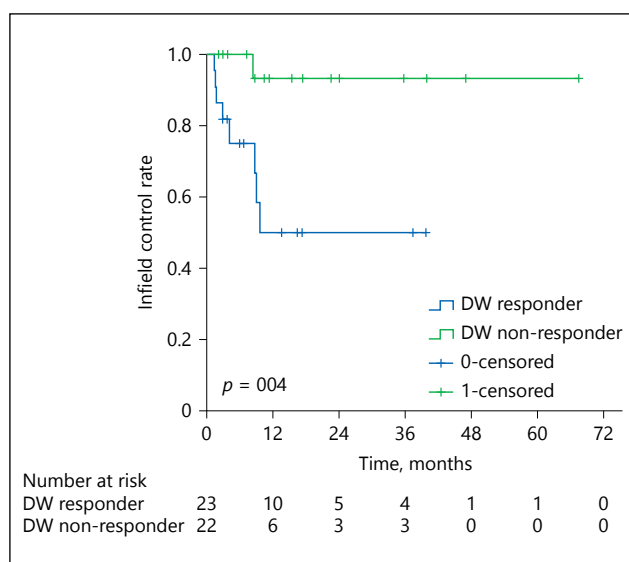


Fig. 1. (for Abstract no P-051).

1.72 ± 0.34 ($\times 10^{-3}$ mm²/s), respectively ($P < 0.001$). An ADC change $\geq 25\%$ (DW[+]) was identified as a predictor of favorable IFC (1-year IFC, 93.3% vs. 50.0% for DW[-], $P = 0.004$), but an mRECIST-based positive response at the first MRI was not ($P = 0.130$). The IFCs of DW(+) SD tumors were not significantly different from those of mRECIST-based responders ($P = 0.327$), whereas DW(-) SD tumors had marginally inferior IFCs to those of mRECIST-based responders ($P = 0.060$). **Conclusions:** ADC change is closely related to IFC in HCCs treated with SBRT. Standardization of the DW MRI protocol, as well as prospective validation studies, are warranted.

P-052

Does the Necessity of More Sessions of Downstaging Treatment of Hepatocellular Carcinoma Prior to Liver Transplantation Pose a Higher Potential of Postoperative Recurrence?

Kuo-Shyang Jeng¹, Chun-Chieh Huang¹,
Chien-Kuan Lin¹, Chien-Chu Lin¹, Chung-Tsui Huang¹,
Chen-Shuan Chung¹, Meng-Tzu Weng¹, Kuo-Hsin Chen¹

¹Far Eastern Memorial Hospital, Taiwan

Introduction: Downstaging (DS) treatment of hepatocellular carcinoma (HCC) prior to liver transplantation (LT) to meet the Milan Criteria or UCSF criteria is an accepted strategy.

Material and Methods: From January 2011 to July 2014, 27 patients with HCC who had received pre-LT downstaging treatments were enrolled into this study. All of them signed

the informed consent. The donors of them included deceased donors ($n = 4$) and living related donors ($n = 23$). After downstaging prior to LT, HCCs of all the patients met with the Milan or UCSF criteria from the pre-LT imagings. The downstaging included 11 resections in 10 patients (2 sessions in one); 48 TACE in 17 patients (1 to 8 sessions individually); one RFA in one patient and 4 PEIT in one patient. The treatment modality and sessions were tailored to each according to patient characteristics (the general condition, cirrhotic degrees, compliance, etc.), tumor characteristics (location, number, procedure feasibility, etc.), and the previous treatment response. Eighteen patients received two or more different therapies. The treatment effect is compared in the size and the number before DS and after DS from radiological imagings. The factors of 6 patients with recurrent LT recurrence

Table 1. Recurrence of HCC after transplantation (for Abstract no P-052)

	Recurrence		p-value
	Yes (n = 6) 20.7 %	No (n = 23)	
Age	56.0±10.4	7.4±6.2	1.0
Gender			1.0
Male	6 (22.2)	21 (77.8)	
Female	0	2 (100)	
MELD score	7.7±1.5	10.0±3.8	0.174
No. of tumor (before DS)			1.0
≤3	10 (40.0)	15 (60.0)	
≥4	1 (25.0)	3 (75.0)	
No. of tumor (after DS)			1.0
0	1 (50.0)	1 (50.0)	
1	6 (37.5)	10 (62.5)	
2	3 (37.5)	5 (62.5)	
3	1 (33.3)	2 (66.7)	
Effect of DS assessed by no.			0.164
Success	2 (11.1)	16 (88.9)	
Failure	4 (36.4)	7 (63.6)	
Size of HCC			
Before DS	5.1±2.6	3.9±2.2	0.302
After DS	4.7±3.2	2.7±1.7	0.174
Transplant explants	4.1±3.5	3.2±2.5	0.618
Effect of DS assessed by size			1.0
Success	3 (20.0)	12 (80.0)	
Failure	3 (21.4)	11 (78.6)	
No. of TACE			0.390
≤2	2 (13.3)	13 (86.7)	
≥3	4 (28.6)	10 (71.4)	
No. of total treatment			0.633
≤2	1 (10.0)	9 (90.0)	
≥3	5 (26.3)	14 (73.7)	
No. of total treatment			0.056
≤4	2 (10.0)	18 (90.0)	
≥5	4 (44.4)	5 (55.6)	

No: number; DS: downstaging; TACE: transcatheter hepatic arterial chemoembolization; (): %.

were analyzed. **Results:** Among the factors affecting recurrence, total sessions of downstaging treatment more than 5, the P value was 0.056 (Table 1). **Discussion and Conclusion:** If the downstages need more than 5 session to fulfill L.T. criteria, the potential risk of recurrence becomes higher. It means the original tumor burden before DS still affects the recurrence after L.T. To select patients for L.T., this factor could be an important consideration.

P-053

Multicenter Phase II Study of Stereotactic Ablative Radiotherapy for Hepatocellular Carcinoma within the Milan Criteria (KROG 12-02)

WON IL JANG¹, Mi-Sook Kim¹, Kwang Mo Yang¹, Chul-Koo Cho¹, Hyung Jun Yoo¹, Jin Kyu Kang¹, Eun Kyung Paik¹, Eun Ji Kim¹, Chul Won Choi², Ah Ram Chang³, Young Hee Park³, Eun Seog Kim⁴, Sunmi Jo⁵, Woonchul Kim⁶, Jeong Hoon Park⁶, Sun Hyun Bae⁷, Hae Jin Park⁸

¹Korea Institute of Radiological and Medical Sciences, Korea, ²Dongnam Institute of Radiological & Medical Sciences, Korea, ³Soonchunhyang University Seoul Hospital, Korea, ⁴Soonchunhyang University Cheonan Hospital, Korea, ⁵Haeundae Paik Hospital, Korea, ⁶Inha University Hospital, Korea, ⁷Soonchunhyang University Bucheon Hospital, Korea, ⁸Hanyang University Hospital, Korea

Purpose: The purpose of this study is to evaluate the efficacy of stereotactic ablative radiotherapy (SABR) for hepatocellular carcinoma (HCC) within the Milan criteria. **Material and Methods:** A total of 54 patients with unresectable HCC showing an incomplete response after 1-5 sessions of transarterial chemoembolization were enrolled in a phase II clinical

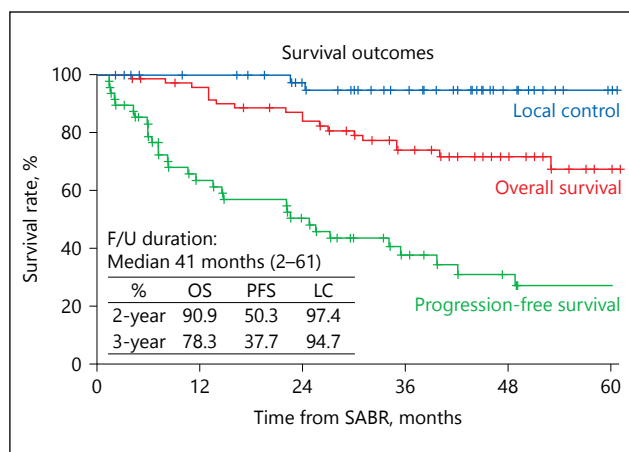


Fig. 1. (for Abstract no P-053).

trial of SABR from 6 institutions between July 2012 and June 2015. SABR was delivered with a total dose of 60 Gy in 3 fractions within 14 days. The treatment response was evaluated using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Radiation-induced liver disease (RILD) was analyzed. Survival outcomes were analyzed with the Kaplan-Meier method. This trial is registered with ClinicalTrials.gov, number NCT01825824. **Results:** Forty-eight patients were evaluable with a median follow-up of 41 months (range, 2–61 months). The median tumor size was 2.0 cm (range, 1.0–4.5 cm) and most patients (89.6%) had a single lesion. Thirty-six patients underwent 1 or 2 TACE sessions. Local control rates at 2 and 5 years were 97.4% and 94.7%, respectively. Overall survival rates at 2 and 5 years were 90.9% and 78.3%, respectively. Progression-free survival rates at 2 and 5 years were 50.3% and 27.0%, respectively. One patient experienced non-classic RILD with acute toxicity. **Conclusion:** The high-dose SABR for HCC within the Milan criteria is and effective as evidenced by the high rates of tumor control, overall survival, and acceptable treatment-related toxicity.

Biomarkers / Cell Biology and Translational Research

P-054

Limited Bias Effect of Intratumoral Heterogeneity on Genetic Profiling of Hepatocellular Carcinoma

Ao Huang¹, Xin-Rong Yang¹, Jia Fan¹, Jian Zhou¹

¹Zhongshan Hospital, Fudan University, China

Introduction: Profiling tumor for genetic variations potentially indicative of target drugs could provide new hope for patients with advanced cancer, such as hepatocellular carcinoma (HCC). However, intratumoral heterogeneity (ITH) challenges comprehensive genotyping and may lead to treatment failure. This study aims to evaluate whether and to what extent would genetic profiling be biased by ITH in HCC. **Methods:** Publications focusing on ITH of HCC were included and clinicopathological parameters and sequencing data were extracted make data reanalysis. The genetic variations were classified according to our previously reported standards as well as the measurement of ITH extent. Actionable genes were identified as if the protein product of a genomic aberration could be potentially targeted by a specific targeted drug. Potential therapeutic targets and driver genes in HCC were

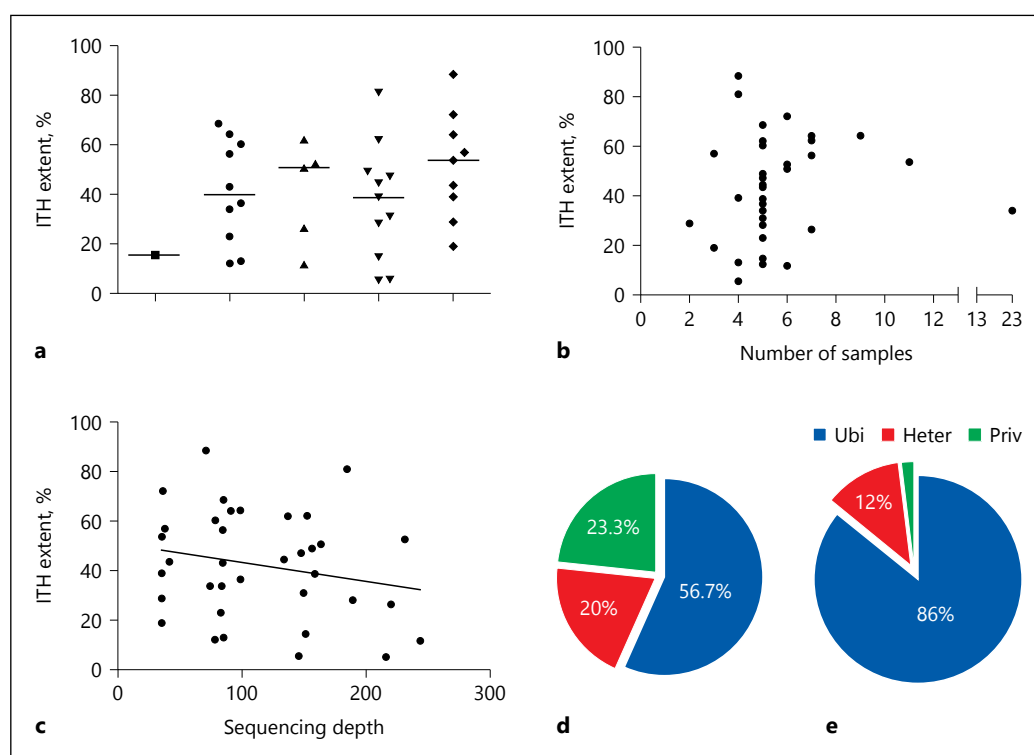


Fig. 1. (for Abstract no P-054).

also pooled as reference to analyze the bias effect of ITH on genetic profiling. **Results:** Totally, 72 genes were identified to be associated with treatment response of target drugs. Literature retrieval identified five studies concerning the genetic ITH of HCC, using NGS of multi-site samples. In total, 207 tumor samples from 36 HCC patients were enrolled. The ITH ranged from 5.21% to 88.27% and no correlations between ITH extent and sample numbers, sequencing depth, and tumor clinicopathological parameters existed. Seventy-two therapeutic and 15 candidate driver genes were pooled as reference. Totally, 38.8% HCCs were found to be drugable in single-site sample, of which only 19.4% might be biased by ITH. Of the driver genes, 86% could be detected in single-site sample. **Conclusions:** ITH varied significantly in HCC but it has limited influences on identification of actionable and driver mutations and might not be a major obstacle in target therapy. Single-site biopsy/sampling based targeted deep sequencing may be enough and of high cost-effectiveness.

P-055

Predictive Value of Peripheral Blood Immune Profiling in Advanced Hepatocellular Carcinoma

Yi-Ping Hung^{1,2}, Yee Chao^{1,2}

¹Taipei Veterans General Hospital, Taiwan, ²National Yang-Ming University, Taiwan

Background: Recent progress in cancer immunology provides more insight in immune evasion of cancer cells. Cancer cells may achieve immune evasion through several ways including ineffective antigen presentation, T cell checkpoint utilization, immunosuppressive cytokines secretion and immunosuppressive cells recruitment. Few literatures mentioned about the change of peripheral blood immune cells in advanced hepatocellular carcinoma (HCC) patients. To answer this question, we initiated a pilot study through detailed flow cytometry. **Method:** We enrolled patients with advanced HCC patients in CHECKMATE-040 clinical trials with informed consent to the collection of their peripheral blood. We also recruited healthy individuals for the control group. Using flow cytometry, we analyzed lymphocyte subclasses and the PD-1 or PD-L1 positivity of immune cells in peripheral blood from HCC patients and healthy individuals. **Results:** Twenty-four HCC patients were enrolled and twenty healthy individuals were enrolled. Most of the HCC patients

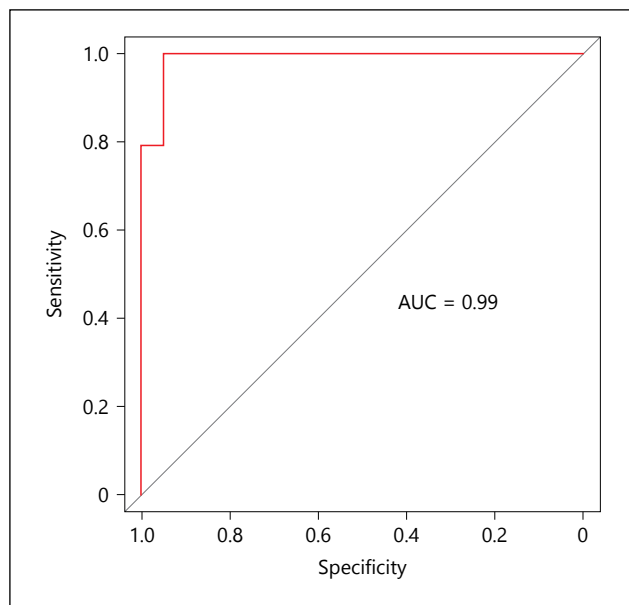


Fig. 1. (for Abstract no P-055).

were HBV carrier (58.3%) (table 1), and the mean age was 61 years old. Among 55 immune cell parameters we examined in peripheral blood, 16 were significantly different between advanced HCC patients and healthy individuals by univariate analysis. Multivariate analysis was then conducted by fitting logistic regression model and showed that CD69-CD25- Naive on CD4 $\alpha\beta$ T cell percentage and dendritic cell percentage can reasonably predict the advanced HCC status from peripheral blood. By our regression model, the adjusted generalized $R^2 = 0.918$ (Table 3) and the estimated area under the Receiver Operating Characteristic (ROC) curve was 0.99 (Figure 1). **Conclusion:** CD69-CD25- Naive on CD4 $\alpha\beta$ T cell percentage and dendritic cell percentage in peripheral blood are highly correlated with the advanced HCC status. The change may result from immune evasion initiated by HCC cells and further investigation is warranted. Validation study is ongoing and this mechanism may be utilized for treatment in the future.

P-056

CD38 Predicts Response to Immune Checkpoint Inhibitors in Hepatocellular Carcinoma (HCC)

David Tai^{1,3}, Siting Goh², Harry Ng³, Valerie Chew^{3,4}, Sherlly Lim², Jeffrey Lim^{2,8}, Xin Ni Sim^{2,5}, Huihua Li^{6,7}, Josh Loh², Khin Sabai², Clara Ong², Tracy Loh², Wei Qiang Leow², Joycelyn Lee¹, Han Chong Toh^{1,3}, Ser Yee Lee^{3,9}, Pierce Chow^{3,9}, Fabio Malavasi¹¹, Evan Newell¹⁰, Su Pin Choo^{1,3}, Tony Lim², Joe Yeong^{2,8,10}

¹Division of Medical Oncology, National Cancer Centre Singapore, Singapore, ²Division of Pathology, Singapore General Hospital, Singapore, ³Duke-NUS Medical School, Singapore, ⁴SingHealth Translational Immunology and Inflammation Centre, Singapore, ⁵Temasek Polytechnic, Singapore, ⁶Division of Medicine, Singapore, ⁷Centre for Quantitative Medicine, Duke-NUS Medical School, Singapore, ⁸Institute of Molecular Cell Biology, Agency of Science, Technology and Research, Singapore, ⁹Department of Hepatopancreatobiliary and Transplant Surgery, Singapore General Hospital, Singapore, ¹⁰Singapore Immunology Network, Agency of Science, Technology and Research, Singapore, ¹¹Laboratory of Immunogenetics and CeRMS, Department of Medical Sciences, University of Torino, Italy

Background: Anti-PD-1 immune checkpoint inhibitors (ICI) have been found to be efficacious in a proportion of patients with advanced hepatocellular carcinoma (HCC). There remains no predictive biomarker of response. Adenosine-ergic (CD38-CD203a-CD73) pathway represents an alternative immunosuppressive mechanism to PD-1/PD-L1. We sought to determine the expression of CD38 on immune and tumour cells in HCC and its relationship with response to anti-PD-1 ICI. **Method:** 44 annotated archival formalin-fixed, paraffin-embedded (FFPE) specimens taken prior to ICI were studied. Multiplex immunohistochemistry (IHC) was performed using an Opal Multiplex IHC kit (PerkinElmer, Inc., Waltham, MA, USA). Tissue microarray (TMA) sections were labelled with primary antibodies against CD38, CD8 and CD68. A Vectra 3 pathology imaging system microscope (PerkinElmer, Inc.) was used to obtain images, and these were analysed using inForm software (version 2.4.2; PerkinElmer, Inc.). **Results:** Tumour, lymphocytes and macrophages express CD38. Macrophages represent the largest CD38+ immune cell subset in HCC. CD38+ immune infiltrate subsets within the tumour was strongly associated with a positive response to anti-PD-1 ICI (responsive vs. non-responsive, 15.835.943% vs. 3.5391.070%; $p = 0.0041$). CD38+ lymphocytes (responsive vs. non-responsive, 26.1310.84% vs. 4.4951.437%; $p = 0.0034$) was strongly associated with better responsiveness but not CD38+ macrophages (responsive vs. non-responsive, 5.5362.521% vs. 2.5821.049%; $p = 0.2160$). The optimal cut-off for CD38+ leukocyte proportion using receiver oper-

ating characteristic (ROC) analyses was 4.4% positive out of total immune infiltrates, and this cut-off achieved 75.0% accuracy, 73.3% specificity and 80.0% sensitivity with area under curve (AUC) of 0.867. **Conclusion:** CD38+ leukocyte proportion potentially predicts response to anti-PD-1 ICI in HCC. This warrants further evaluation.

Viral Hepatitis / Cirrhosis and Related Complications

P-057

Tenofovir and Entecavir has Similar Renal Adverse Events on Hepatocellular Carcinoma Patients Treated with Transarterial Chemoembolization

Young Youn Cho¹, Young Hwan Choi¹, Su Jong Yu², Eun Ju Cho², Jeong-Hoon Lee², Yoon Jun Kim², Jung-Hwan Yoon²

¹Department of Internal Medicine, Chung-Ang University Hospital, Korea, ²Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Korea

Background/Aims: Tenofovir has potential nephrotoxicity in chronic hepatitis B patients. Hepatocellular carcinoma (HCC) patients treated by transarterial chemoembolization (TACE) are in high risk of renal injury. The aim of this study is

to find if tenofovir has more renal adverse events compared to entecavir in HCC patients treated with TACE. **Methods:** In this retrospective single center study, we selected 53 HCC patients treated with tenofovir from January 2012 to July 2013 and performed their first TACE in the same period. The patients were matched by age and sex to patients treated with entecavir. We analyzed creatinine increase, eGFR decrease, and dose reduction of antiviral agents. **Results:** There were no significant differences of baseline characteristics including HCC factors, nephrotoxic drug use, and number of contrast imaging studies between the two groups. Median follow-up period was 17.0 and 20.0 month for the tenofovir group and the entecavir group, respectively. There was no difference in creatinine increase over 0.5 mg/dL (17.0% and 17.0%, $P = 1.00$), and eGFR decrease over 25% (43.4% and 41.5%, $P = 0.84$) during the follow-up period in the tenofovir group and the entecavir group, respectively. By multivariate analysis, Child-Pugh class over B (Hazard ratio [HR], 7.30; 95% confidence interval [CI] 2.79–19.10; $P < 0.01$) was associated with creatinine increase, and Child-Pugh class over B (HR, 82.74; 95% CI 12.31–555.83; $P < 0.01$) and Barcelona-Clinic Liver Cancer stage over B (HR, 14.93; 95% CI 1.60–139.51; $P = 0.02$) were associated with eGFR decrease. **Conclusions:** Tenofovir is a safe treatment in HCC patients undergoing TACE compared with entecavir.

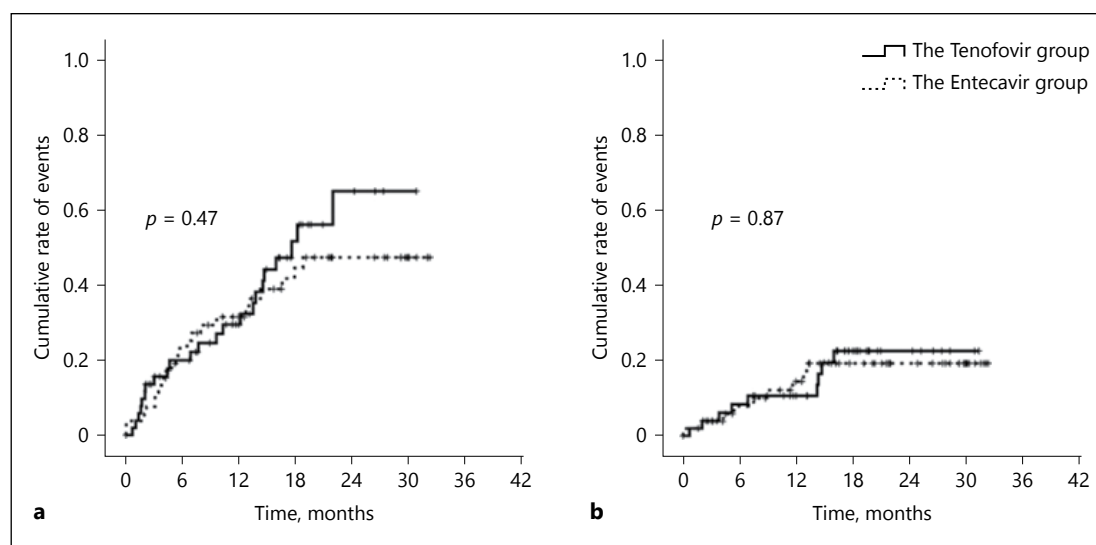


Fig. 1. Renal events of the tenofovir group compared to the entecavir group. **a** Kaplan-Meiercurve of eGFR decrease over 25%. **b** Kaplan-Meiercurve of creatinine increase over 0.5 mg/dL (for Abstract no P-057).

P-058

Real State of Antiviral Therapy in the Patient with Hepatitis C Related Hepatocellular CarcinomaHyun Young Woo¹, Jeong Heo¹, Young Joo Park¹,
Young Mi Hong¹, Ki Tae Yoon¹, Mong Cho¹¹Pusan National University Hospital, Korea

Background/Aim: In spite of the great improvement of antiviral therapy with highly effective and safe direct-acting antiviral (DAA) agents, real state of DAA treatment in patients with HCV related hepatocellular carcinoma (HCC) has not been investigated so far. **Methods:** Until December 2018, all patients with HCV related HCC have been investigated for the types and outcome of antiviral therapy, modalities for HCC treatment, status of HCC during antiviral treatment and change of liver function after antiviral therapy. **Results:** Total 278 were treated with HCC associated with HCV. Of them, 124 have not been treated for HCV due to advanced HCC (n = 32), not covered by medical insurance (n = 59), poor medical condition (n = 16) and follow up loss (n = 17). The others (n = 154) were treated with interferon (IFN) (n = 44) or DAA (n = 110). Of 44 with IFN, 31 were treated median 64 months (range, 8–243 months) before development of HCC (SVR 64.5%) and 13 were treated after complete remission (CR) with HCC treatment (SVR 69.2%). Of 110 with DAA, 34 were treated for HCV median 12 months (range, 3–43 months) before development of HCC (SVR 88.2%) and 76 were treated after CR after (n = 54) (SVR 88.8%) or during HCC treatment (n = 22) (SVR 86.3%). After DAA treatment, liver function was improved from Child-Pugh class B to class A in 38.5% (5/13). In patients with CR, HCC recurrence rate was 61.5% (8/13) in IFN and 57.4% (31/54) in DAA. Median time to HCC recurrence is 33 month (95% CI, 0–67.9 months) after IFN and 7

month (95% CI, 0–14.3 months) after DAA (P = 0.131). **Conclusions:** Treatment in patients with HCC was not inferior to those without in terms of efficacy and safety. Close HCC surveillance would be needed in patients with cirrhosis soon after DAA treatment.

P-059

Cumulative Incidence of Hepatocellular Carcinoma and Hepatitis B Surface Antigen Seroclearance After Nucleos(t)ide analogue Induced Hepatitis B Antigen SeroclearanceHyun Woong Lee¹, Saein Kim¹, Jung Il Lee¹,
Kwan Sik Lee¹¹Yonsei University College of Medicine, Gangnam Severance Hospital, Korea

Backgrounds and Aim: Hepatitis B e antigen (HBeAg) seroclearance in the long term has been viewed as a treatment endpoint and a measurement of treatment success. We tried to determine the clinical outcomes for hepatocellular carcinoma (HCC), and hepatitis B surface antigen (HBsAg) seroclearance of patients undergoing nucleos(t)ide analogue induced HBeAg seroclearance. **Methods:** The current study included patients who required antiviral treatment (entecavir or tenofovir) before and/or after HBeAg seroclearance, within a tertiary care setting. Patients with documented HBeAg seroclearance were followed up 6-monthly. Baseline characteristics and longitudinal laboratory results were recorded. **Results:** Cumulative incidence for HCC and HBsAg seroclearance were derived from Kaplan-Meier method. A total of 219 patients underwent HBeAg seroclearance with a median age and follow-up of 50 and 4.2 years, respectively. The cumulative incidence of HCC and HBsAg seroclearance was 10.8%

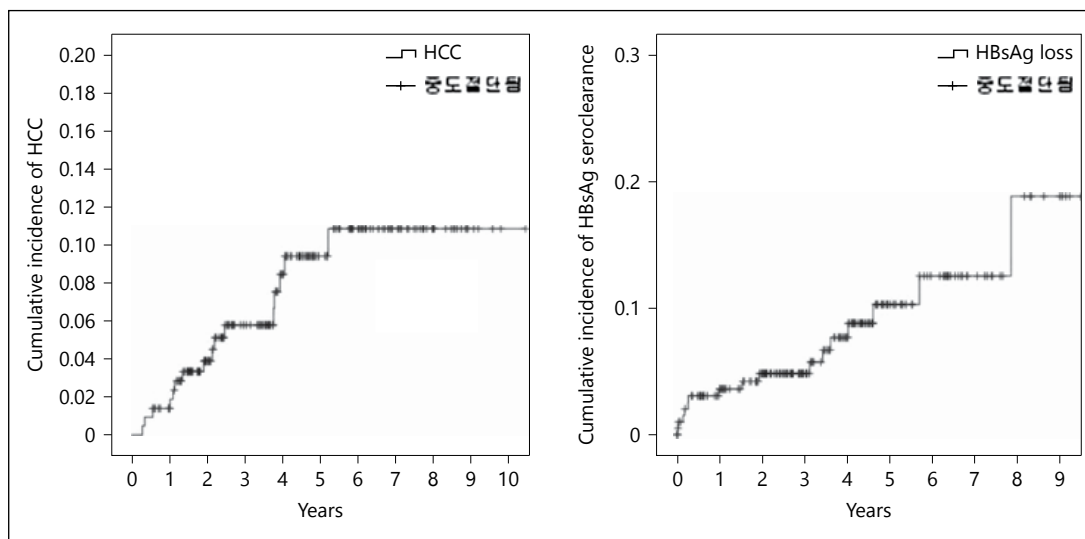


Fig. 1. (for Abstract no P-059).

and 18.7% at 9 years after HBeAg seroclearance, respectively.

Conclusion: A small proportion of patients who undergo nucleos(t)ide analogue induced HBeAg seroclearance achieved HBsAg seroclearance. However, a significant proportion of patients will develop hepatocellular carcinoma after HBeAg seroclearance.

Diagnosis and Liver Imaging / Epidemiology and Surveillance / Miscellaneous

P-060

Targetoid Mass on Gadoteric Acid-Enhanced MRI Using LI-RADS v2018: Emphasis on Hepatocellular Carcinomas Assigned to the LR-M Category

Hyun Jeong Park¹, Young Kon Kim²

¹Chung-Ang university hospital, Korea, ²Samsung medical center, Korea

Aim: To determine useful imaging features for differentiating hepatocellular carcinoma (HCC) categorized as LR-M from non-HCC malignancies using Liver Imaging Reporting and Data System (LI-RADS) v2018 on gadoteric acid-enhanced MRI (Gd-EOB-MRI). **Methods:** Patients at high risk for HCC with surgically confirmed HCCs ($n = 131$) and non-HCC malignancies ($n = 90$) and who had undergone Gd-EOB-MRI were included. LI-RADS categories were assigned to identify hepatic observations defined as LR-M by two radiologists. Major and ancillary imaging features of targetoid observations including intratumoral septum were compared between HCCs and non-HCC malignancies. A classification tree analysis (CTA) was applied to differentiate high-risk HCCs from non-HCC malignancies in the LR-M category. **Results:** A total of 36 HCCs (27.5%) and 70 non-HCC malignancies (77.8%) were assigned as LR-M. Enhancing capsule ($p = 0.0293$), blood products in mass ($p = 0.0393$), non-targetoid restriction ($p = 0.018$), and septum ($p = 0.0053$) were significantly predictive of HCC. On CTA, septum was an initial predictor for a high probability of HCC followed by non-targetoid restriction. The CTA model has a sensitivity of 63.9%, specificity of 90.0%, and accuracy of 81.1% for differentiating HCC assigned LR-M from non-HCC malignancy. **Conclusion:** A considerable proportion of HCCs could be categorized as LR-M as they had a targetoid appearance on Gd-EOB-MRI. Intratumoral septum and non-targetoid restriction as well as enhancing capsule and blood products in mass may be useful for differentiating HCC assigned LR-M from non-HCC malignancy on Gd-EOB-MRI.

P-061

Inter-Reader Agreement of the LI-RADS for the Diagnosis of Hepatocellular Carcinoma on MRI: A Systematic Review and Meta-Analysis

Ji Hun Kang¹, Sang Hyun Choi¹, Seong Ho Park¹,
Kyung Won Kim¹, So Yeon Kim¹, Seung Soo Lee¹,
Jae Ho Byun¹

¹Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Korea

Aim: We aimed to determine the inter-reader agreement of Liver Imaging Reporting and Data System (LI-RADS) on contrast-enhanced MRI. **Methods:** The MEDLINE and EMBASE databases were searched from January 2014 through December 2018 to identify original articles reporting the inter-reader agreement of LI-RADS on MRI. We calculated the meta-analytic pooling intra-class correlation coefficient (ICC) for lesion size and kappa value (κ) for major features (arterial-phase hyperenhancement [APHE], nonperipheral washout [WO], and enhancing capsule [EC]), and LI-RADS categorization (LR) using random-effects model. Meta-regression analysis and subgroup analysis were performed to explore the cause of study heterogeneity. **Results:** Fifteen articles with a total of 2968 lesions were included. The meta-analytic pooled ICC of lesion size was 0.97 (95% confidence interval [CI]: 0.94, 1.00). The meta-analytic pooled κ of APHE, WO, EC, and LR were 0.72 (95% CI: 0.62, 0.82), 0.69 (95% CI: 0.60, 0.78), 0.66 (95% CI: 0.58, 0.75), and 0.70 (95% CI: 0.56, 0.85), respectively. Substantial study heterogeneity was noted in all five variables ($I^2 \geq 89.1\%$, $P < 0.001$). Study design, type and clarity of blinding review were significant factors for study heterogeneity ($P \leq 0.05$). LI-RADS version 2017 showed higher agreements of APHE (0.74 vs. 0.70), EC (0.72 vs. 0.64), and LR (0.80 vs. 0.67) than version 2014. Senior readers had a higher agreement of LR (0.72 vs. 0.57) than junior readers, but lower agreements of APHE (0.69 vs. 0.82) and WO (0.66 vs. 0.76). **Conclusion:** LI-RADS demonstrated overall good inter-reader agreement with a substantial agreement for major features and LR, and almost perfect for lesion size.

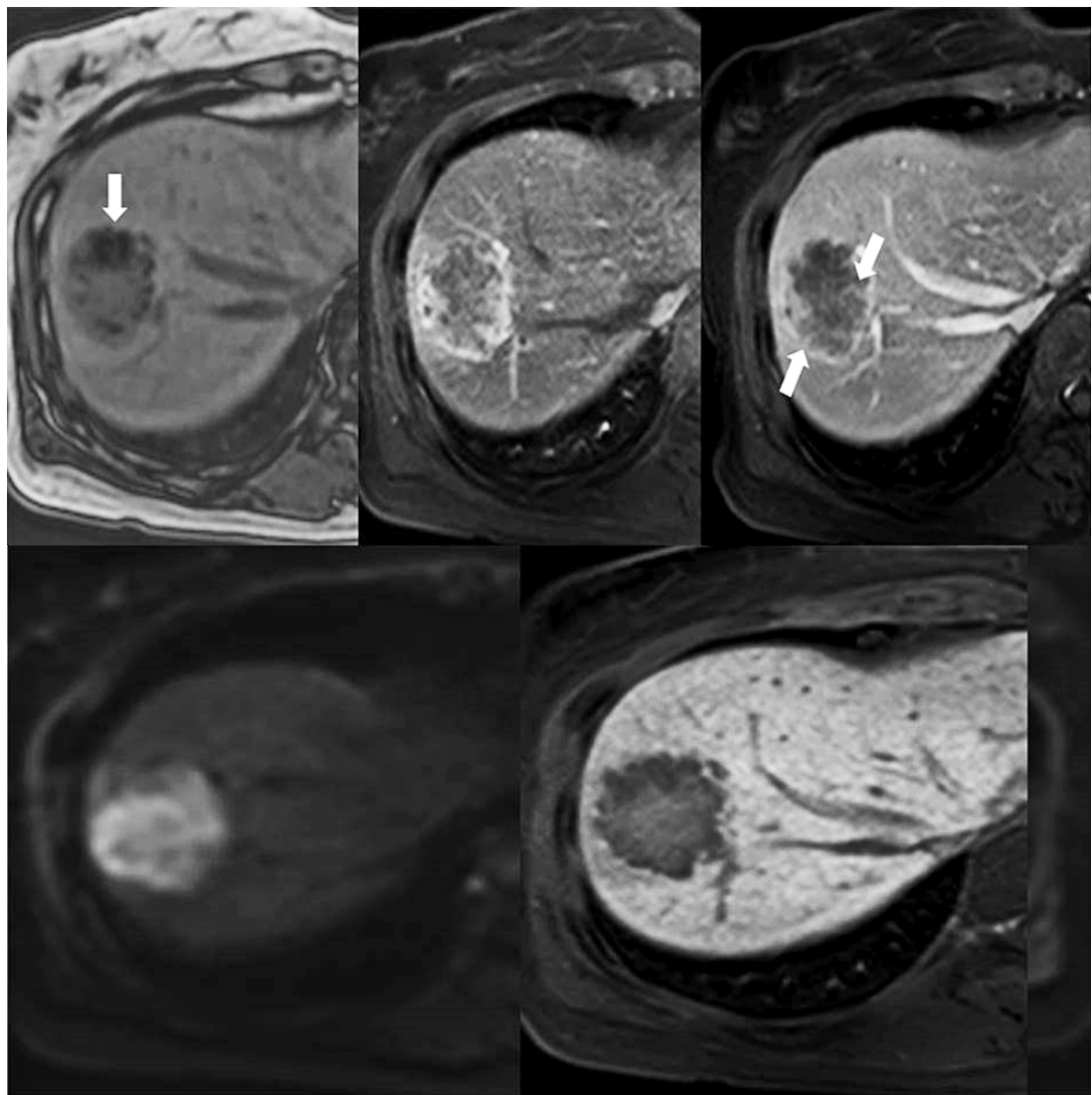


Fig. 1. (for Abstract no P-060).

P-062

Associations Between Tumor Gene Expression, Fluorocholine PET/CT Imaging Phenotype, and Post-Resection Survival in Early-Stage Hepatocellular Carcinoma

Sandi A. Kwee¹, Linda L. Wong¹, Miles M. Sato², Maarit I. Tiirikainen¹

¹University of Hawaii Cancer Center, USA, ²The Queen's Medical Center, USA

Background: Several gene expression signatures seem to predict tumor recurrence and overall survival in hepatocellular carcinoma (HCC). Recent studies have also suggested that tumor uptake of fluorine-18 fluorocholine, a radiopharmaceutical analog of choline used for PET/CT imaging of HCC,

may also be predictive of clinical outcomes. We compared tumor fluorocholine uptake with tumoral expression of prognostic gene signatures in patients with early-stage HCC treated by hepatic resection. **Methods:** With written informed consent, 35 patients with HCC completed fluorocholine PET/CT prior to tumor resection and whole-genome expression profiling of tumor samples. A prognostic signature for surgically-resectable HCC was tested by proportional hazards regression analysis and compared with tumor fluorocholine uptake. **Results:** All tumors were classified by the survival signature at a false discovery rate (FDR) <0.05. Overall survival differed significantly between resulting bad and good survival groups (mortality odds-ratio (OR) 4.3, 95% CI 1.55–13.7). Tumor to liver fluorocholine uptake ratio (TLR), quantified by PET/CT, also differed significantly between these groups (0.85 vs. 1.45, $p < 0.0001$). A TLR <1.0 (ie. low tumor

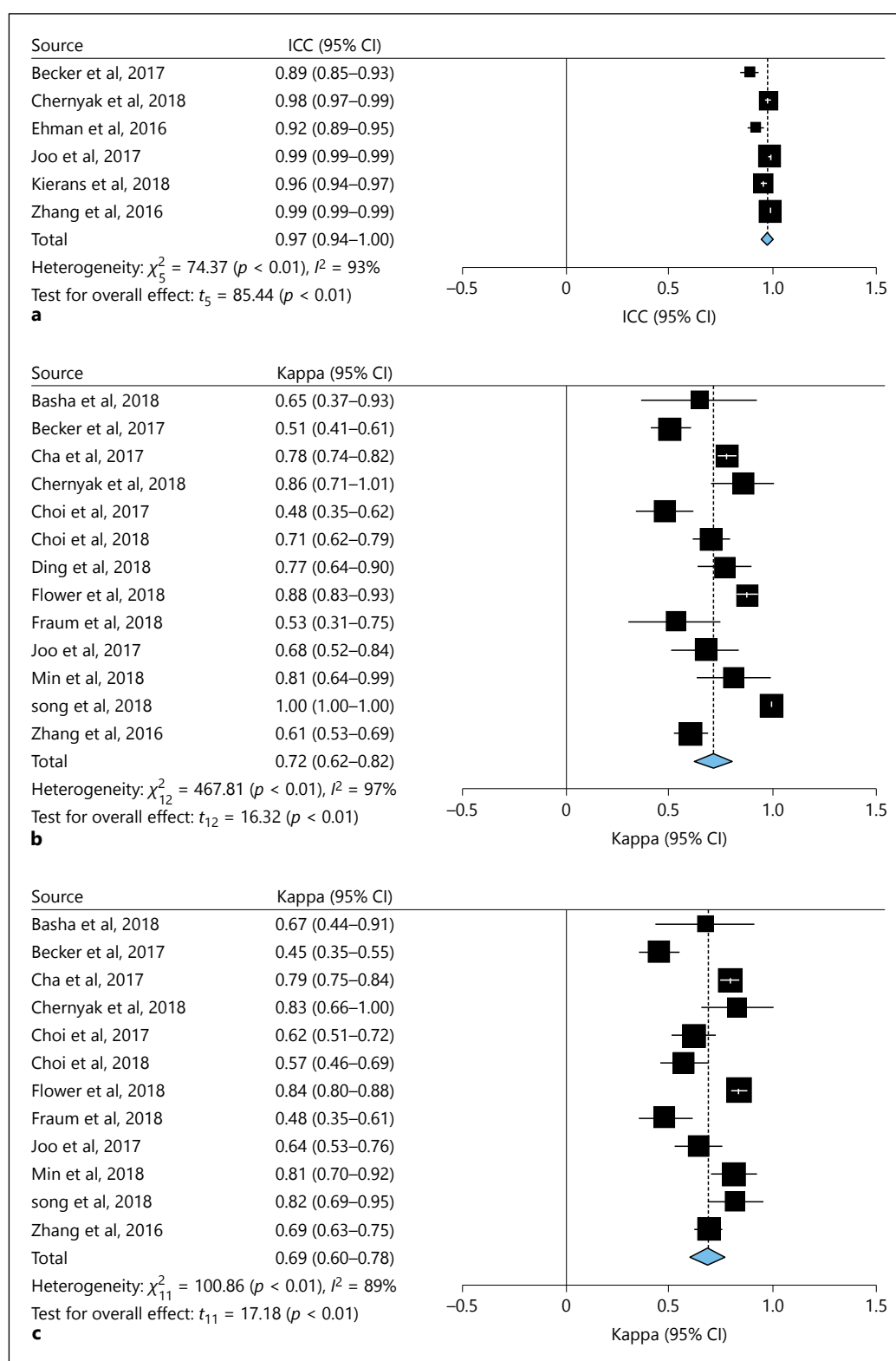


Fig. 1. Meta-analytic pooled inter-reader agreement of LI-RADS. **a** Lesion size; **b** Arterial phase hyper-enhancement; **c** Nonperipheral washout; **d** Enhancing capsule; **e** LI-RADS categorization (for Abstract no P-061).

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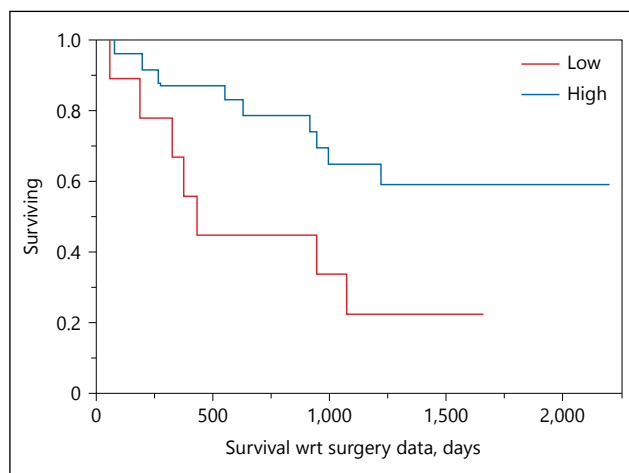
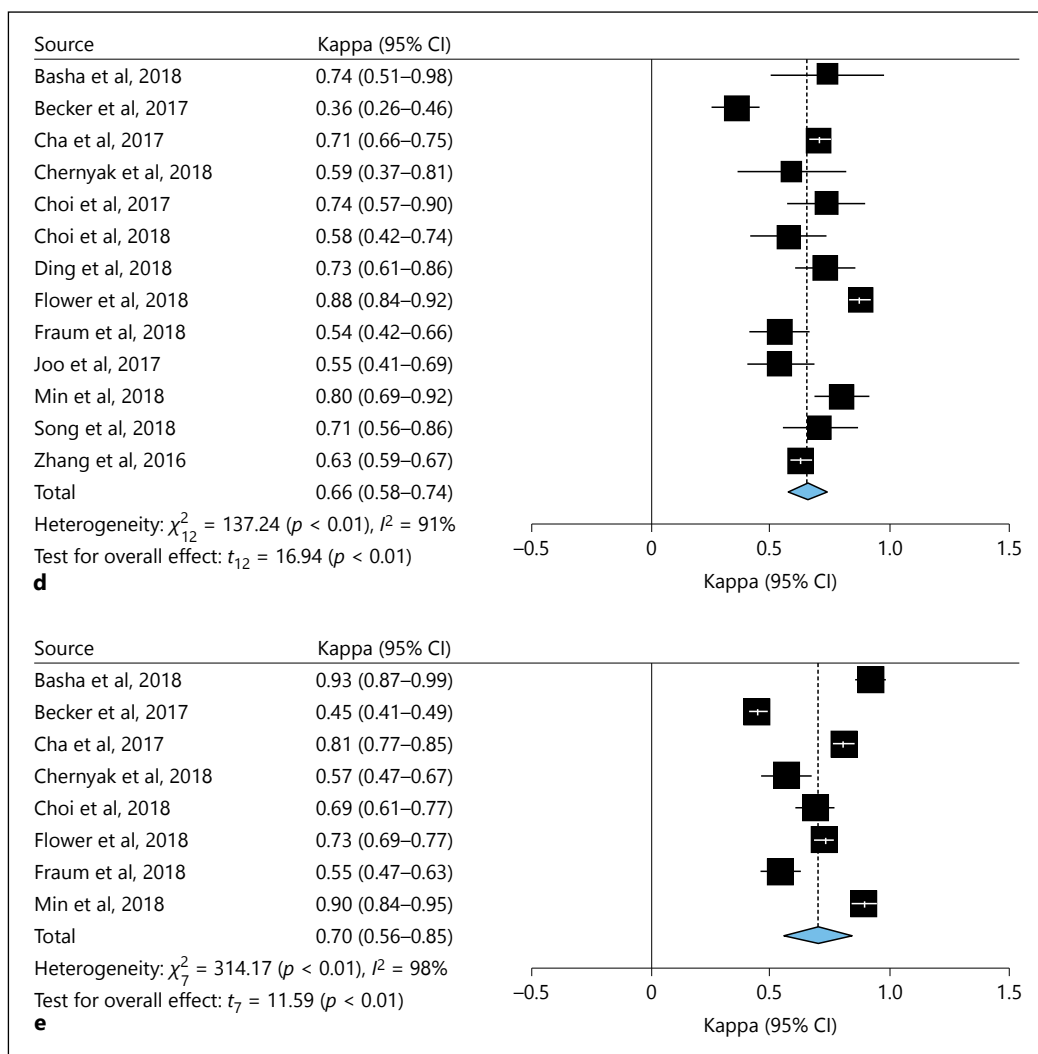


Fig. 1. Survival plot (for Abstract no P-062).

fluorocholine uptake) was associated with higher mortality risk (OR 3.1, 95% CI 1.1–8.4). However, tumor size was the most robust predictor of mortality in multivariate adjusted analyses (age- and gender- adjusted OR 9.1, 95% CI 2.1–55.0). Poor survival and low tumor fluorocholine uptake were associated with tumoral over-expression of genes associated with glycolysis and hypoxia (FDR <0.0001). **Conclusion:** The potential prognostic value of fluorocholine PET/CT in HCC may be associated with specific patterns of tumor gene expression. However, the clinical value of PET/CT imaging and tumor molecular profiling as prognostic markers should be considered in the context of other known clinical biomarkers.

P-063

Change in the Recurrence Pattern and Risk Factors Over Time after the Complete Cure of Hepatocellular Carcinoma: Ten-Year Follow-Up Study

Han Ah Lee¹, Seung Up Kim², Hyun Gil Goh¹,
Tae Hyung Kim¹, Sun Young Yim¹, Young-Sun Lee¹,
Sang Jun Suh¹, Young Kul Jung¹, Ji Hoon Kim¹,
Yeon Seok Seo¹, Hyung Joon Yim¹, Jong Eun Yeon¹,
Kwan Soo Byun¹, Soon Ho Um¹

¹Korea university medical center, Korea, ²Yonsei University College of Medicine, Korea

Background/Aim: Recurrence pattern and risk factors for recurrence after complete cure of hepatocellular carcinoma (HCC) changes over time. However, there were only few studies evaluated the recurrence of HCC in time-dependent analysis. **Methods:** All patients with first diagnosed Barcelona-Clinic Liver Cancer (BCLC) stage A HCC which were completely cured with surgical resection or radiofrequency ablation (RFA) at Korea University Hospital and Yonsei University Severance Hospital were included between 2007 and 2016. **Results:** In total, 1,496 patients who were cured from BCLC stage A HCC with surgical resection or RFA were included. Liver cirrhosis was combined in 919 patients (61.4%). Type of treatment was surgical resection in 991 patients (63.5%) and

RFA in 570 patients (36.5%). The change of recurrence pattern over time is presented in Figure 1. Patient population and risk factors for HCC recurrence also changed with the time progression. In patients without HCC recurrence within 1 year, combined liver cirrhosis, treated with RFA, number and size of tumors, and MELD score were the independent risk factors for HCC recurrence at 1 year after treatment for HCC. While, in patients without HCC recurrence within 3 years, age, combined liver cirrhosis, and treated with RFA were the independent risk factors for HCC recurrence at 3 years after treatment for HCC. Combined cirrhosis and treatment type were two independent risk factors for HCC recurrence in almost time points. When patients were classified into four groups according to the presence of liver cirrhosis and the type of treatment, the cumulative incidences of HCC recurrence decreased with time progression in all groups, but the recurrence rate at the same time point was significantly different between groups. **Conclusion:** Recurrence pattern and risk factors for recurrence after complete cure of HCC changes with time progression. Appropriate surveillance strategy is needed.

P-064

Potential Etiology, Prevalence of Cirrhosis, and Mode of Detection among Patients with Non-B Non-C Hepatocellular Carcinoma in Korea

Jihye Kim¹, Wonseok Kang¹, Dong Hyun Sinn¹,
Geum-Youn Gwak¹, Yong-Han Paik¹, Moon Seok Choi¹,
Joon Hyeok Lee¹, Kwang Cheol Koh¹, Seung Woon Paik¹

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

Background/Aim: We systematically evaluated the clinical characteristics, prevalence of cirrhosis, and mode of detection in virus-unrelated (non-B non-C, NBNC) HCC patients in Korea. **Methods:** A total of 447 consecutive treatment-naïve NBNC-HCC adult patients who were registered at the Samsung Medical Center HCC registry in Korea from 2010 to 2013 were analyzed. NBNC was defined as negative HBsAg and negative anti-HCV antibody. Presence of cirrhosis was determined based on histological, radiological, endoscopic, and serologic results. Mode of detection was classified as either under surveillance, incidental, or symptomatic. **Results:** Heavy alcohol use was the most common potential etiology in NBNC-HCC (NBNC-A, alcohol) (59.7%). Ten patients had other identifiable causes (NBNC-O, other identifiable cause) such as autoimmune hepatitis. The rest (38.0%) had no-identifiable cause (NBNC-NA-NO, non-alcohol, no-other identifiable cause). In NBNC-NA-NO group, 83.5% (96/115) of patients with available hepatitis B core immunoglobulin G antibody (HBcIgG) showed HBcIgG positivity, and

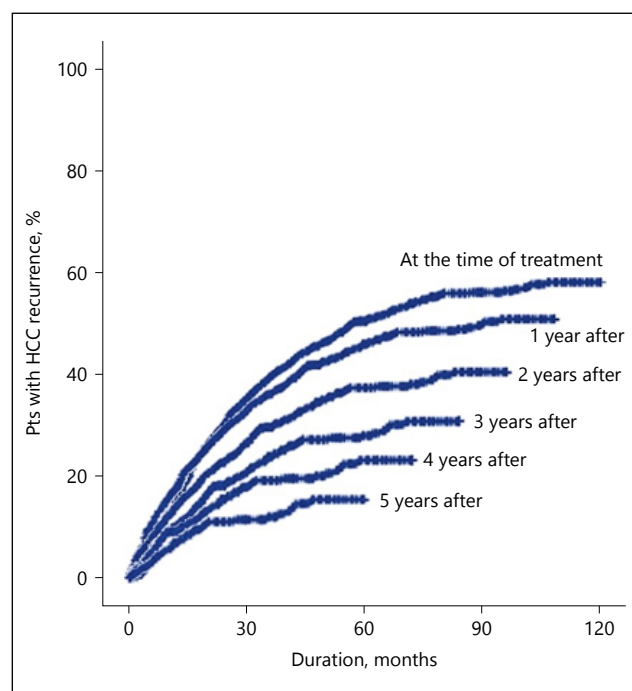


Fig. 1. The cumulative incidence of HCC recurrence at the time of resection or RFA, and at 1, 2, 3, 4, and 5 years after resection or RFA (for Abstract no P-063).

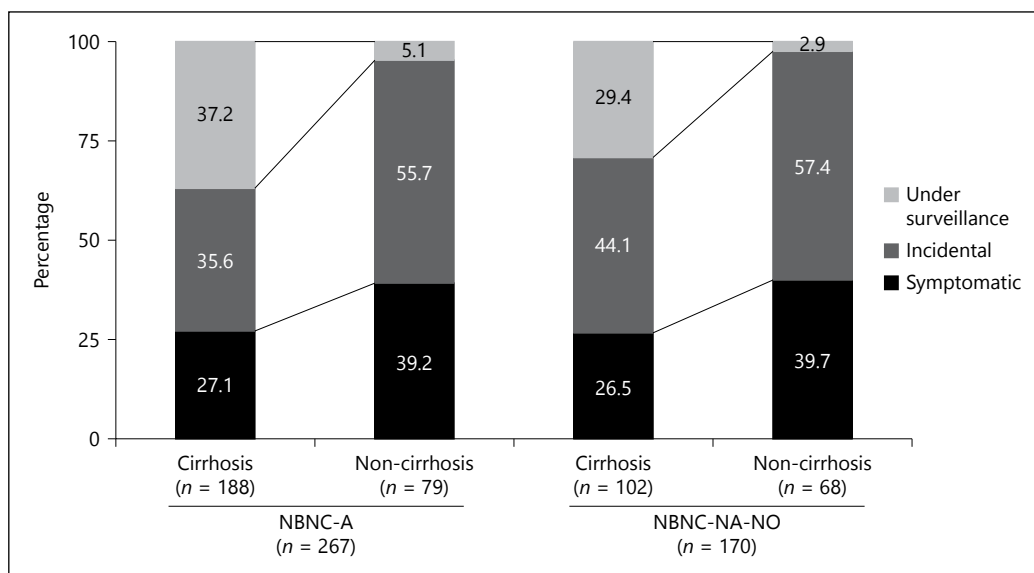


Fig. 1. (for Abstract no P-064).

80.6% (137/170) had metabolic risk factors (diabetes, obesity, hypertension and/or dyslipidemia). Cirrhosis was present in 90.0%, 70.4%, and 60.0% of NBNC-O, NBNC-A, and NBNC-NA-NO patients, respectively. The proportion of patients diagnosed under surveillance was 25.5% across all patients, with specific proportions being 80.0%, 27.7%, and 18.8% for NBNC-O, NBNC-A, and NBNC-NA-NO, respectively.

Conclusion: Among NBNC-HCC patients, heavy alcohol use or any other identifiable cause was not found in 38.0%. These NBNC-NA-NO HCC patients showed a high prevalence of HBcIgG positivity and metabolic risk factors, suggesting that prior HBV infection and metabolic risk factors may be major contributing factors in the hepatocarcinogenesis in NBNC-NA-NO patients.

P-065

The Impact of HBsAg and HBeAb on Noninvasive Diagnostic Criteria for Hepatitis B Virus-Related Hepatocellular Carcinoma

Bei Tang¹, Zhenggang Ren¹

¹Zhongshan Hospital, Fudan University, China

Aim: This study aims for verification of liver cirrhosis-based HCC diagnostic criteria in a hepatitis B virus (HBV) prevalent population and exploration in improvement by HBV markers serostatus. **Methods:** A retrospective analysis was conducted of 348 cases of resections and biopsies for liver nodules at Zhongshan hospital, Shanghai, China. Data were collected from a prospectively developed database. Patients newly detected liver lesions (≥ 1 cm) with histological confirmation were enrolled and divided into HCC group (191 patients) and non-HCC group (157 patients). Both groups were allocated randomly into derivation set (HCC, n = 122 vs. non-HCC, n = 100) and validation set (HCC, n = 69 vs. non-HCC, n = 57). Diagnostic criteria models were constructed concerning image features, α -fetoprotein serum levels and HBV serostatus, and assessed by sensitivity, specificity and the area under the receiver operating characteristic curve. Optimal diagnostic tests were derived with the use of derivation data set and were verified with the use of validation data set. **Results:** A diagnostic modality concerning seropositive HBV surface antigen or HBV envelope antibody and α -fetoprotein serum levels more than 20 ng/ml but no cirrhotic liver performed sensitivity, specificity and the area under the receiver operating characteristic curve 64%–84%, 91%–95%, 0.792–0.869, respectively, with no significant difference from AASLD criteria for HCC diagnosis (70%, 95%,

0.821). **Conclusions:** Liver cirrhosis, although required in AASLD diagnostic criteria, is not inevitable in diagnosing HCC in an HBV prevalent population. A complication modality of increased serum α -fetoprotein, seropositive hepatitis B surface antigen or hepatitis B envelope antibody might help improve diagnostic ability for HBV related HCC lesions.

P-066

A Significant Diagnostic Role for Discrimination of Malignancy of Contrast Enhanced Ultrasound for Portal Vein Thrombosis in HCC Patients

Jung Hyun Kwon¹, Yu Ri Shin¹, Sun Hong Yoo¹, Soon Woo Nam¹

¹The Catholic University of Korea, Korea

Background: The characterization of portal vein thrombosis (PVT) as malignant versus bland is of great significance for therapeutic strategy in the patients with HCC. The aim is to investigate quantitative time-intensity curve (TIC) parameters and qualitative CEUS characteristics for differentiation between benign and malignant PVT, compared to the diffusion-weighted MRI (DWI). **Methods:** A total of 50 HCC patients who showed the PVT in liver dynamic CT or MRI were consecutively enrolled and performed CEUS. TIC parameters were analyzed and DWI was performed using b values of 0, 400 and 800 sec/mm² at 3-T unit. A thrombus was diagnosed as malignancy if it was enhanced on MRI. **Results:** There were 19 bland thrombi and 31 malignant thrombi in 50 patients as the diagnostic enhancement of MRI. All qualitative parameters of CEUS such as arterial-phase enhancement, washout in the venous phase, vessel occlusion and expansion were significantly more common in malignant thrombosis than benign thrombosis ($p < 0.05$). Regarding quantitative parameters of CEUS, shortened time to maximum enhancement, increased area under the TIC, prolonged time between the half amplitude values in each side of the maximum, prolonged the time from injection until the peak of enhancement in malignant thrombosis, were seen compared to benign thrombosis. These parameters were correlated with tumor stage and PIVKA II ($p < 0.05$). A strong correlation was found between DWI-MRI and CEUS ($p < 0.0001$). After an additional CEUS evaluation, 3 patients with the enhancement PVT on MRI were considered bland thrombus, in contrast, 4 patients with no enhancement PVT on MRI were considered malignant thrombus. Overall follow-up period, 5 of 7 patients consistent with the diagnosis of CEUS. **Conclusion:** The present study showed that CEUS is comparable high diagnostic accuracy to DWI-MRI. Some TIC parameters by CEUS are useful for characterization of PVT in the patients with HCC.

P-067

Role of Contrast Enhanced Ultrasound in Surveillance for Hepatocellular Carcinoma: A Pictorial Review

Carmen Cho¹, Stella Ho¹, Brian Yuen¹, Stephanie Yip¹, Esther Hung¹

¹Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China

Objective: Contrast enhanced ultrasound (CEUS) offers unique advantages in the characterization of focal liver lesions and enables characterization of indeterminate nodules identified on routine B mode ultrasound surveillance of hepatocellular carcinoma (HCC). Hence it is increasingly integrated into the diagnostic algorithm for HCC in centres across the world. This poster describes the incremental role of CEUS in HCC surveillance as well as demonstrates how CEUS can differentiate among commonly encountered focal liver lesions through illustrative examples. **Materials and Methods:** We retrospectively reviewed 87 cases of CEUS liver with Sulphur hexafluoride microbubbles. Representative images were selected for case illustration. **Results:** We demonstrate how the dynamic, real-time enhancement pattern on CEUS can discriminate among various focal liver lesions, including regenerative nodule, dysplastic nodule, hemangioma, focal fatty sparing, focal fatty infiltration, focal nodular hyperplasia-like nodule, hepatocellular carcinoma, cholangiocarcinoma, and metastasis. The inclusion of CEUS in the diagnostic algorithm of HCC has unique advantages over CT or MRI, due to its superior sensitivity to detect arterial hypervascularity, detailed assessment of arterial phase filling patterns, and discriminatory features of washout. Thus, CEUS is able to offer a one-stop exclusion of typical benign liver lesions, precluding the need for subsequent more costly investigations. **Conclusion:** Through its unique properties, CEUS can provide added value in characterizing focal liver lesions, thus potentially serving as a one-stop gateway during ultrasound surveillance for HCC.

P-068

The Clinical Behavior and Survival of Patients with Hepatocellular Carcinoma and a Family History of the Disease

Ju Hyun Shim¹, Seheon Chang¹, Ha Il Kim¹, Han Chu Lee¹

¹Asan Medical Center, Korea

Background and Aims: Familial clustering is a common feature of hepatocellular carcinoma (HCC) as well as a risk factor for the disease. We aimed to assess whether such a family history affected prognostic outcomes in patients with HCC diagnosed at different stages of the disease. **Methods:**

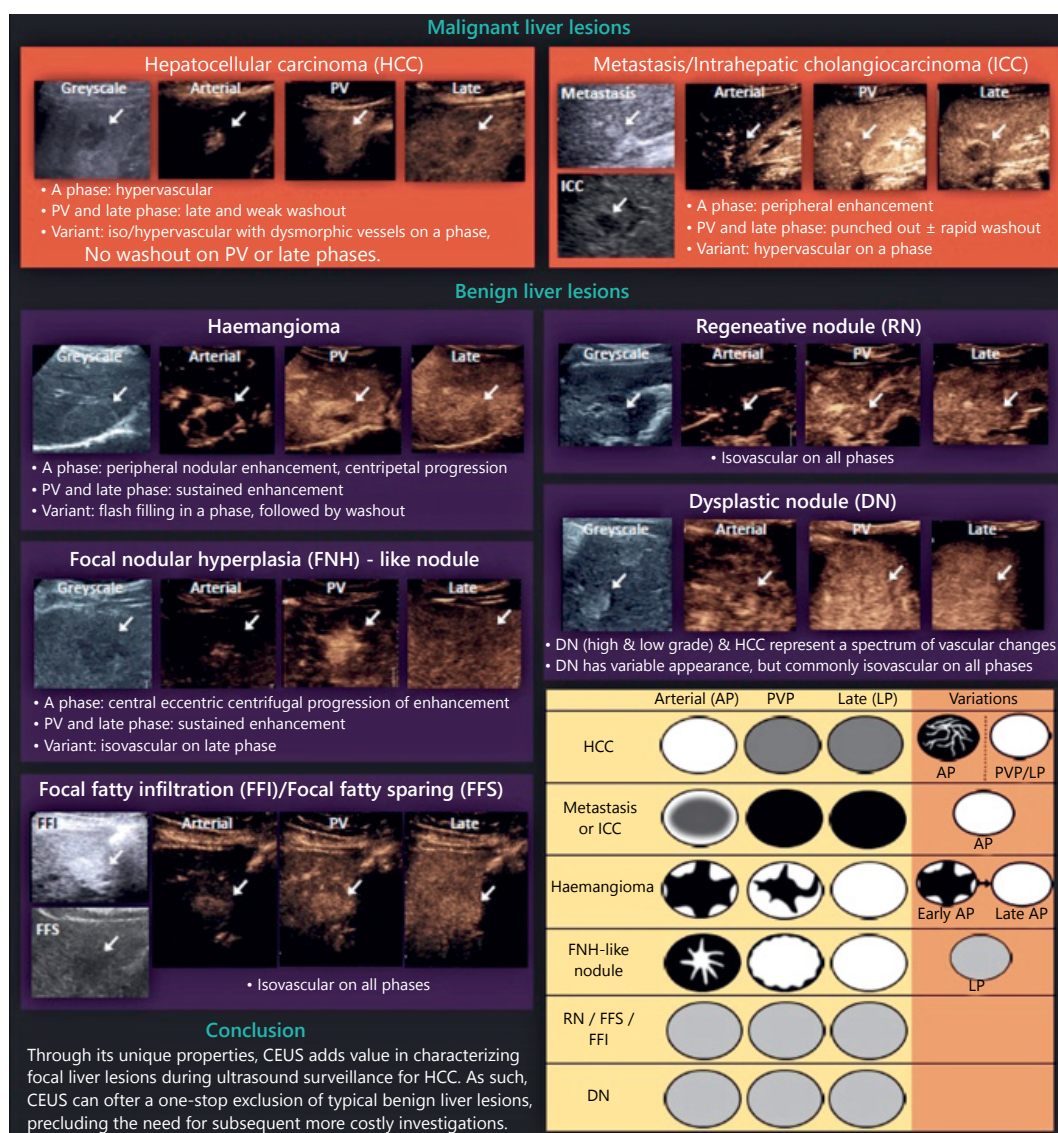


Fig. 1. (for Abstract no P-067).

This hospital registry-based cohort study included 5,484 patients initially diagnosed with HCC. Individual family histories of cancer were obtained by interview and reported by trained nurses who constructed three-generation pedigrees. Overall survival data were compared between cases with and without first-degree relatives affected by HCC, with adjustment for other potential predictors. **Results:** Of 5,484 patients, 845 (15.4%) had first-degree relatives with a history of HCC. A family history was associated with longer survival in the entire cohort (adjusted hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.80–0.98, $P = 0.025$). A significant trend for reduced risk of death with increasing number of affected family members was also observed (P for trend = 0.018). Stage-stratified analysis showed that the presence of a family history was especially associated with a reduced risk of death

in the subset of patients with HCC at a (very) early stage (adjusted HR 0.83, 95% CI 0.69–0.99; $P = 0.042$). The proportion of cases receiving curative treatment was also higher in early-stage patients with a family history (72.6% vs. 63.3%; $P < 0.001$). **Conclusion:** A first-degree family history of the disease is a prognostic factor for improved survival in patients with HCC, especially in those whose tumors can be cured by radical treatments.

Molecular Pathogenesis and Pathology / Staging and Prognosis

P-069

A Case of Transitional Liver Cell Tumor in a 10-Year-Old Boy

Momoko Ara¹, Shohei Honda¹, Takafumi Kondo¹, Kazuyoshi Okumura¹, Hiromi Okada², Emi Takakuwa², Hirokazu Sugino³, Akinobu Taketomi¹

¹Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Japan, ²Department of Surgical Pathology, Hokkaido University Hospital, Japan, ³Department of Cancer Pathology, Faculty of Medicine, Hokkaido University, Japan

Introduction: The most common hepatic malignancy in children is hepatoblastoma (HB) and the majority of cases arise before age of 3. Malignant hepatic tumors in the adolescent or early adult population are also rare, and they show some common characteristics in molecular, histologic, and clinical findings as found in HB. These tumors are termed transitional liver cell tumors (TLCTs). **Case Report:** A previously healthy 10-year-old boy who presented with abdominal pain and nausea was referred to our hospital due to shock symptoms because of active intraabdominal hemorrhage with a large right-sided hepatic mass. The blood pressure of the patient on admission was 70/45 mm Hg and the pulse rate was 140 beats per minute. His hemoglobin level was 6.8 mg/dL and liver function test findings were normal. A computed tomography (CT) scan revealed a 8.5 cm x 8.0 cm x 6.0 cm hyper-vascular solid mass in segment 6 of the liver and no evidence of metastasis in other organs. Emergent hepatic angiography and transcatheter arterial embolization (TAE) were performed with 4 units of RBC transfused. AFP (3615.2 ng/mL) and PIVKA-II levels (1493 mAU/mL) were significantly elevated. Complete tumor resection by partial hepatectomy was performed 6 days after TAE. A rupture site at the inferior surface of the tumor was seen in operation. Pathologically, the tumor was diagnosed as a malignant hepatocellular tumor consisting of both HCC and HB components. He has been receiving standard adjuvant chemotherapy for HB, cisplatin/pirarubicin (CITA), and there has been no evidence of recurrence by imaging findings and tumor markers for 10 months after surgery. **Discussion:** TLCT is extremely rare and known to show poor prognosis. An effective treatment algorithm has not been established, and regular examination and early detection of signs of recurrence is important.

P-070

LncRNA CCAT2 Genetic Polymorphisms are Associated with Susceptibility to Hepatocellular Carcinoma

Kuan-Chun Hsueh¹, Shun-Fa Yang², Shih-Chi Su²

¹Tungs Taichung MetroHarbor Hospital, Taiwan,

²Chung Shan Medical University, Taiwan

Background and Objectives: The global incidence of hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is heterogeneous due to the variable prevalence of etiological factors, indicating a correlation of HCC risk with genetic variations among individuals. Among long non-coding RNAs (lncRNAs) located in the chromosome 8q24 loci and involved in the carcinogenesis are colon cancer associated transcript 2 (CCAT2) and cancer susceptibility candidate 8 (CASC8). **Methods:** In this study, the association of CCAT2 and CASC8 gene polymorphisms with the occurrence of HCC was assessed between 397 HCC patients and 1195 controls. **Results:** We found that homozygotes for the minor allele (GG) of CCAT2 rs6983267 were more susceptible to HCC, with the OR and AOR being 1.532 (95% CI, 1.103–2.129; p = 0.011) and 1.462 (95% CI, 1.031–2.074; p = 0.033), respectively. Moreover, for patients stratified by age (under 65), gender (male only), or status of drinking (habitual drinkers), a protective effect of CASC8 rs3843549 on presenting high Child-Pugh scores, metastatic vascular invasion, or large-size tumors was observed. **Conclusion:** In conclusion, our data reveal association of CCAT2 and CASC8 gene polymorphisms with the incidence and progression of liver cancer.

P-071

A Case of Fibrolamellar Hepatocellular Carcinoma Successfully Treated with Surgical Resection

Seong Kyun Na¹, Byung-Cheol Song¹, Young-Kyu Kim¹, Sun Mi Lee¹

¹Jeju National University Hospital, Korea

Background: The fibrolamellar hepatocellular carcinoma (HCC) accounts for 1% of all primary liver cancers. Unlike typical HCC, fibrolamellar HCC occurs in young patients without underlying liver disease. **Methods:** A case report and literature review. **Results:** A 19-year-old female without underlying chronic liver disease visited the outpatient clinic because of abnormal liver enzyme levels from two years ago. The laboratory examination showed elevated liver enzyme tests (AST 66 IU/L, ALT 106 IU/L, alkaline phosphatase 602 U/L). The abdominal ultrasonography showed 13 cm sized lobulated mass in the right liver. The levels of AFP and CA 19-9 levels were within normal range. The magnetic resonance

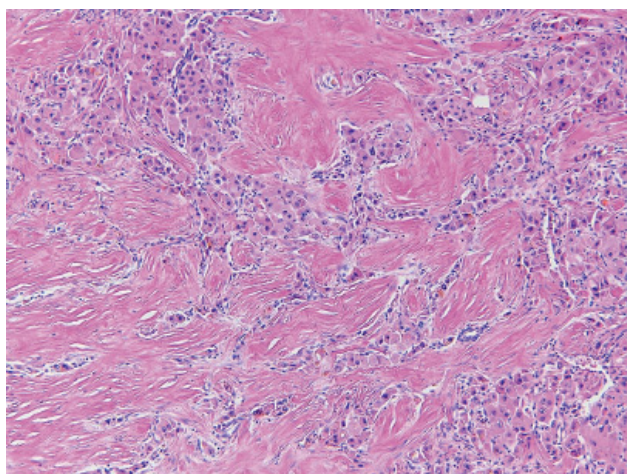


Fig. 1. (for Abstract no P-071).

imaging (MRI) showed lobulated liver mass with central scar and prominent arterial enhancement and low signal intensity on delayed and hepatobiliary phase. The biopsy result showed large, polygonal cells with abundant eosinophilic cytoplasm and fibrous stroma arranged in parallel lamellae around tumor cells. Tumor was diagnosed as fibrolamellar HCC. The right hemihepatectomy was performed and she was followed up for 7 months without recurrence. Discussion: Fibrolamellar HCC is a very rare primary liver tumor, which is not associated with chronic viral hepatitis or liver cirrhosis. AFP level is usually normal. The DNAJB1-PRKACA fusion gene in chromosome 19 is detected in nearly all cases. Surgical resection is a mainstay of treatment. **Conclusion:** We report a case of fibrolamellar HCC which was successfully treated with surgical resection.

Treatment: Systemic, Targeted, Novel Target or Experimental Therapy

P-072

Efficacy and Safety of Nivolumab after Failure of Sorafenib for Advanced Hepatocellular Carcinoma (HCC): A Prospective Cohort Study

KyungHye Bang¹, Changhoon Yoo¹, YunJin Hong¹, Kyu-pyo Kim¹, Baek-Yeol Ryoo¹

¹Asan Medical Center, University of Ulsan College of Medicine, Korea

Background: Nivolumab showed promising anti-tumor efficacy in HCC in prior phase I/II CheckMate-040 trial. We analyzed clinical outcomes of HCC patients enrolled in our biomarker prospective cohort and treated with nivolumab. **Methods:** 27 patients with unresectable or metastatic HCC who received nivolumab after failure of sorafenib in Asan Medical Center, Seoul, Korea, between May 2018 and April 2019, were included. Nivolumab was given at 3 mg/kg intravenously, every 2 weeks. Response and adverse events (AEs) were graded according to the RECIST v1.1 and NCI CTCAE v4.03. **Results:** Median age was 58 years and 81.5% (n = 22) were male. 81.5% (n = 22) had HBV infection and 70.4% (n = 19) were Child-Pugh A. All patients were BCLC stage C, and extrahepatic metastasis and major vascular invasion were detected in 26 (96.3%) and 13 (48.1%), respectively. Median time-to-progression (TTP) on prior sorafenib was 2.5 months (95% CI, 1.2–3.8). Nivolumab was administered as 2nd-, 3rd- and 4th-line treatment in 16 (59.3%), 8 (29.6%) and 3 (11.1%), respectively. The number of treatment cycle was median 4 (range, 1–21). Objective response rate was 11.1% (3/27) and median time-to-response was 1.54 months (range, 1.51–1.74). All of them are ongoing (7.33+ to 8.54+ months) at data cut-off. Median progression free survival (PFS) was 1.71 months (95% CI, 1.59–1.83) and median overall survival (OS) was 6.51 months (95% CI, 2.80–10.22). 6-month PFS and OS rates were 23.7% and 44.9%, respectively. There was no significant difference in survival outcomes according to the number of previous chemotherapy or TTP on prior sorafenib. AEs were consistent with those in prior trials for nivolumab. **Conclusion:** Nivolumab demonstrated clinical benefit and promising long-term duration of response in patients with sorafenib-refractory HCC.

P-073

Factors Associated with Post-Progression Survival in Advanced Hepatocellular Carcinoma Patients with Post-Sorafenib Progression Not Eligible for Regorafenib

Chang Wook Kim^{1,2}, Hee Yeon Kim¹, Sang Wook Choi^{1,2}, Do Seon Song^{1,2}, U Im Chang^{1,2}, Jin Mo Yang^{1,2}, Sung Won Lee^{1,2}, Hae Lim Lee^{1,2}, Nam Ik Han^{1,2}, Sun Hong Yoo^{1,2}, Jung Hyun Kwon^{1,2}, Soon Woo Nam^{1,2}, Pil Soo Sung^{1,2}, Jeong Won Jang^{1,2}, Si Hyun Bae^{1,2}, Jong Young Choi^{1,2}, Seung Kew Yoon^{1,2}

¹The Catholic University of Korea, Korea, ²The Catholic University Liver Research Center, Korea

Background: We aimed to investigate the prognostic factors associated with post-progression survival (PPS) in advanced hepatocellular carcinoma (HCC) patients who showed radiological progressive disease (PD) following sorafenib monotherapy, and were not eligible for 2nd-line regorafenib treatment. **Methods:** A total of 223 patients who were confirmed with radiological PD following sorafenib monotherapy from September 2008 to December 2017 were enrolled. We define those with Child-Pugh class A, ECOG PS 0 or 1 at progression, and who had tolerated sorafenib as candidates eligible for 2nd-line regorafenib therapy. **Results:** Among 223 patients with PD after sorafenib treatment, 126 (56.5%) patients met eligibility criteria for regorafenib treatment at first radiological confirmation of PD. The median PPS of the candidates for regorafenib treatment (12.1 months) was statistically longer ($P < 0.001$) than that of the non-candidates (3.2 months). Prognostic factor associated with good PPS in non-candidates for regorafenib therapy was absence of macrovascular invasion [hazard ratio = 0.5 (95% confidence interval 0.33–0.76)] at initial radiological PD. **Conclusions:** Absence of macrovascular invasion at initial radiological PD following sorafenib may predict good PPS in advanced HCC patients who had progressed after sorafenib monotherapy and were not eligible for 2nd-line regorafenib treatment.

P-074

Unnecessity of Preoperative Transarterial Chemoembolization in Patients with Resectable Hepatocellular Carcinoma

Ho Joong Choi¹, Gun Hyung Na¹, Tae Yun Lee¹, Joseph Ahn¹, Tae Ho Hong¹, Young Kyoung You¹, Dong Goo Kim¹

¹The Catholic University of Korea, Seoul, Korea

Background: Hepatic resection is a cornerstone in the treatment of hepatocellular carcinoma (HCC) patients. In liver transplantation, preoperative transarterial chemoembolization (TACE) with down staging has a good outcome, but it is

doubtful whether resection shows the same result. **Methods:** From January 2005 to December 2015, 274 patients who underwent curative hepatic resection at our center were included. They were divided into the hepatic resection-only (Non-PT) group ($n = 208$, 75.9%) and preoperative TACE (PT) group ($n = 66$, 24.1%). The effect after preoperative TACE was analyzed by changes in the modified response evaluation criteria in solid tumors (mRECIST) and tumor marker expression. **Results:** We found no statistically significant difference in the disease free survival (DFS) ($p = 0.397$) and overall survival (OS) ($p = 0.373$) rates between the Non-PT and PT groups. The Non-PT group and responders in the PT group showed no difference between DFS and OS, but non-responders in the PT group showed significantly worse DFS and OS (mRECIST: $p = 0.029$ for DFS, $p = 0.003$ for OS; AFP: $p = 0.079$ for DFS, $p = 0.002$ for OS). **Conclusions:** Preoperative TACE did not affect the outcome after resection. If there is no response after preoperative TACE, resection should be considered carefully because the postoperative results are statistically poor.

P-075

Magnetic Hyperthermia Effect of Chitosan-Bilirubin Coated Nanoparticle in the Treatment of Hepatocellular Carcinoma

Yong Yeon Jeong¹, Suchithra P Surendran¹, Myeong Ju Moon¹, Kwon Ha Yoon², Jin Hong Kim¹

¹Chonnam National University Hwasun Hospital, Chonnam National University, Korea, ²Wongkwang University Hospital, Korea

Purpose: Magnetic hyperthermia (MHT) is one kind of cancer treatment. Magnetic nanoparticles (MNPs) are representative nanomaterials for MHT cancer treatment due to their biocompatibility and high magnetic susceptibility. MHT may be effective tool to treat the hepatocellular carcinoma (HCC). Chitosan-bilirubin (CB) is found to have ability to undergo a solubility switch from hydrophobic to hydrophilic in response to intrinsic reactive oxygen species (ROS). The aim of this study was to evaluate the MHT effect of CB-coated CoMNP in the treatment of HCC. **Materials and Methods:** Chemical characterizations of synthesized CB-CoMNP were analyzed. Transmission electron microscopy (TEM), dynamic light scattering (DLS), and the particle surface charge were analyzed. In vitro HepG2 cell uptake was confirmed by confocal image and FACS analysis. Cytocompatibility study of CB-CoMNP in NIH3T3 and FL83B cell lines were evaluated. In vivo MFH and tumor reduction study were performed. **Results:** CB-CoMNPs were synthesized by thermal decomposition method. TEM and DLS measurement showed increased size of CB-CoMNP after treatment of ROS generator molecule. Confocal images and FACS showed dose dependent cell uptake of CB-CoMNP in HepG2 cell lines. Cytocompatibility studies of CB-CoMNP showed no toxicity in both NIH3T3 cell line and FL83B cell line. In vivo MFH showed

that 25 mg[Fe]/kg and 50 mg[Fe]/kg CB-CoMNP groups had higher temperature increase than control group. Tumor reduction study also showed that 25 mg[Fe]/kg and 50 mg[Fe]/kg CB-CoMNP groups had better volume reduction than control group. **Conclusion:** This ROS-responsive magnetic CB-CoMNP showed dose dependent uptake of HepG2 cell line in vitro. CB-CoMNP was able to observe tumor targeting and tumor reduction after MHT treatment in the HepG2 model. CB-CoMNP might be used for MHT in HCC treatment.

P-076**Transarterial Infusion of Epirubicin and Cisplatin Combined with Systemic Infusion of 5-Fluorouracil Versus Sorafenib for Hepatocellular Carcinoma with Failure of Transarterial Chemoembolization Using Doxorubicin**

Sunhong Yoo¹, Jung Hyun Kwon¹, Soon Woo Nam¹, Jong Youl Lee¹, Dong Jae Shim¹, Jong Hyun Byeon¹

¹The Catholic University of Korea, Korea

Background and Aim: Transarterial chemoembolization using doxorubicin (TAC-DOX) has been recognized as effective therapy for advanced hepatocellular carcinoma (HCC). However, there are few limited options in the patients with TACE failure. We compared the efficacy of sorafenib and Transarterial chemoembolization using epirubicin and cisplatin combined with systemic infusion of 5-fluorouracil (TAC-ECF) in the patients with TAC-DOX failure. **Method:** We retrospectively analyzed 742 patients who received TAC-DOX as the first-line therapy for HCC between January 2007 and December 2017. Among the patients, 86 patients were received sorafenib or TAC-ECF. TAC-ECF consisted of transarterial infusion of epirubicin and cisplatin combined with systemic infusion of 5-FU. Overall survival and progression-free survival were analyzed. **Result:** The median duration of sorafenib administration was 2.8 months and the median number of TAC-ECF was 2 times. Overall survival after rescue therapy did not differ between sorafenib group and TAC-ECF group (4.7 vs. 6.4 months, $P = 0.730$). Multivariate analysis indicated that CPC B ($P = 0.016$, HR 1.863, 95% CI 1.124–3.087) and BCLC stage C ($P < 0.0001$, HR 2.999, 95% CI 1.653–5.440) influenced shorter overall survival compared to CPC A and BCLC stage B. There was no difference in progression-free survival between the sorafenib group and TAC-ECF group (3.0 vs. 3.5 months, $P = 0.598$). In the multivariate analyses, male patients ($P = 0.034$, HR 1.991, 95% CI 1.054–3.762) and patients with BCLC stage C HCC ($P = 0.035$, HR 1.822, 95% CI 1.044–3.180) showed worse PFS than female patients and patients with BCLC stage B HCC. **Conclusion:** The survival of patients treated with TAC-ECF is consistent with sorafenib in HCC patients with TAC-DOX failure. TAC-ECF might be considered as an alternative therapy for the patients with TAC-DOX failure, especially child-pugh B patients.

Treatment: Clinical Trials**P-077****A Phase 3 Study of Transarterial Chemoembolization Combined with Durvalumab or Durvalumab Plus Bevacizumab in Patients with Locoregional HCC: EMERALD-1**

Masatoshi Kudo¹, Bruno Sangro², Shukui Qin³, Zhenggang Ren⁴, Stephen Chan⁵, Joseph Erinjeri⁶, Yasuaki Arai⁷, Helen Mann⁸, Shethah Morgan⁸, Gordon Cohen⁹, Gordana Vlahovic⁹, Riccardo Lencioni¹⁰

¹Kindai University, Japan, ²Clinica Universidad de Navarra and CIBEREHD, Spain, ³PLA Cancer Center & Bayi Clinical Trial Institute, China, ⁴Zhongshan Hospital, Fudan University, China, ⁵The Chinese University of Hong Kong, Hong Kong SAR, China, ⁶Memorial Sloan Kettering Cancer Center, USA, ⁷National Cancer Center, Tokyo, Japan, ⁸AstraZeneca, Cambridge, UK, ⁹AstraZeneca, Gaithersburg, USA, ¹⁰University of Pisa School of Medicine, Italy

Background/Aims: Since curative therapy is not always feasible and there is no standard systemic therapy, patients with intermediate-stage hepatocellular carcinoma (HCC) are treated with locoregional therapy such as transarterial chemoembolization (TACE). TACE therapy achieves tumor responses, but recurrence is common and often occurs within 1 year. Early evidence shows encouraging activity and durable clinical response for checkpoint inhibitors (CIs), such as durvalumab, as treatment for advanced HCC and combined with TACE. CIs combined with VEGF inhibitors also show promise in advanced HCC. Taken together, combining durvalumab, VEGF inhibitors, and TACE therapies warrants evaluation in patients with locoregional HCC. EMERALD-1 (NCT03778957) is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study assessing efficacy and safety for durvalumab monotherapy when given with either drug-eluting bead (DEB)-TACE or conventional TACE (cTACE) followed by durvalumab ± bevacizumab in patients with HCC not amenable to curative therapy. **Methods:** 600 patients will be randomized 1:1:1 to Arm A (DEB-TACE or cTACE + durvalumab, and followed by durvalumab + placebo), Arm B (DEB-TACE or cTACE + durvalumab followed by durvalumab + bevacizumab), or Arm C (DEB-TACE or cTACE placebo). Durvalumab therapy will begin ≥ 7 days following initial TACE procedure. Durvalumab ± bevacizumab will begin ≥ 14 days following last TACE procedure. Eligible patients must have confirmed HCC not amenable to curative therapy, Child-Pugh score A to B7 and ECOG PS of 0/1. Patients with a history of nephrotic or nephritic syndrome, clinically significant cardiovascular disease, extrahepatic disease, or main portal vein

thrombosis (Vp3/Vp4) are excluded. Patients with active (controlled) or past hepatitis virus B or C infection may be enrolled. The primary endpoint is progression-free survival (PFS) for Arm A versus Arm C by blinded independent radiology review using RECISTv1.1. Secondary endpoints include PFS for Arm B versus Arm C, overall survival, health-related quality of life, and safety.

P-078

Durvalumab With or Without Bevacizumab as Adjuvant Therapy for Patients at High Risk of Recurrence After Curative Therapy: EMERALD-2

Jia Fan¹, Ann-Lii Cheng², Sean Cleary³, Peter Galle⁴, Norihiro Kokudo⁵, Riccardo Lencioni⁶, Joong-Won Park⁷, Jian Zhou⁸, Helen Mann⁹, Shethah Morgan⁹, Xuan Liu¹⁰, Steve Chin¹¹, Gordana Vlahovic¹¹, Jennifer Knox¹²

¹Zhongshan Hospital, Fudan University, China,

²National Taiwan University, Taiwan, ³Mayo Clinic, Rochester, USA, ⁴University Medical Center Mainz, Germany, ⁵National Center for Global Health and Medicine, Japan, ⁶University of Pisa School of Medicine, Italy, ⁷Seoul National Cancer Center, Korea, ⁸Zhongshan Hospital, Fudan University, China, ⁹AstraZeneca, Cambridge, UK, ¹⁰AstraZeneca, China, China, ¹¹AstraZeneca, Gaithersburg, USA, ¹²Princess Margaret Cancer Centre, University of Toronto, Canada

Background/Aim: Hepatic resection and ablation are standard-of-care for patients with hepatocellular carcinoma (HCC), but while potentially curative, the risk of recurrence is high (44%–79% at 5 years). No effective adjuvant therapy currently exists and the prevention and/or delay of recurrence of HCC after curative treatment presents a high unmet medical need. Encouraging evidence suggests that adjuvant therapy involving agents that engage the immune response, including immunotherapy such as durvalumab (an anti-PD-L1 antibody), can prolong recurrence-free survival (RFS) in patients with early-stage HCC. Additionally, VEGF pathway inhibition may enhance activity of PD-L1 blockade in patients with HCC. EMERALD-2 (NCT03847428) is a Phase 3 randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of durvalumab with or without bevacizumab as adjuvant therapy in patients at high risk of recurrence after curative resection or ablation. **Methods:** Approximately 888 patients will be randomized 1:1:1 to Arm A (durvalumab+bevacizumab), Arm B (durvalumab+placebo), or Arm C (placebo+placebo) following curative therapy. Stratification will be based upon evidence of pathological microvascular invasion and geographic region. Eligible patients must have confirmed HCC and successfully completed curative therapy with imaging to confirm disease-free status $\leq$ 28 days prior to randomization, ECOG PS 0–1, and Child-Pugh score of 5 or 6. Exclusion criteria

include prior systemic anticancer therapy for HCC; known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC; metastatic, macrovascular invasion, or co-existing malignant disease at baseline; portal vein thrombosis; waiting for liver transplantation. Patients with hepatitis virus B or C (HBV, HCV) may be enrolled; HBV+ patients must have adequate viral suppression prior to enrollment and HBV/HCV replication will be monitored and treated if appropriate. The primary endpoint is RFS as assessed by blinded independent central radiology review using RECISTv1.1. Secondary endpoints include 2- and 3-year RFS, time to recurrence, overall survival, health-related quality of life, and safety.

Treatment: Surgical Resection and Transplantation

P-079

Improved Outcomes of Laparoscopic Liver Resection for Hepatocellular Carcinoma Located in Posterosuperior Segments of the Liver

Jai Young Cho¹, Yujin Kwon², Ho-Seong Han¹, Boram Lee¹

¹Seoul National University, Korea, ²Seoul Medical Center, Korea

Background: Laparoscopic liver resection (LLR) is widely adapted for hepatocellular carcinoma (HCC), while LLR in PS segments is still challenging. However, with recent improvement of techniques and accumulation of experiences, LLR in PS segments is feasible. We compared outcomes of LLR for HCC located in posterosuperior (PS) segments before and after the adaptation of technological improvements. **Method:** We retrospectively analyzed 149 patients who underwent LLR for HCC located in PS segments from September 2003 to December 2016. The patients were divided into group 1 (n = 43) and group 2 (n = 106) who underwent LLR before and after 2012, when advanced techniques including use of intercostal trocars, Pringle maneuver, and semi-lateral position of patient were adapted. We also compared these patients with those who underwent open liver resection (OLR; n = 124) for HCC in PS segments at the same period. **Results:** Mean operative time (395 minutes vs 331 minutes; P = 0.013), intraoperative blood loss (1545 ml vs 1219 ml; P = 0.020), and hospital stay (12 days vs 9, P < 0.001) were significantly less in group 2. Postoperative complication rate (18.6% vs 18.9%; P = 0.970), open conversion rate (23% vs 17%; P = 0.374), 5-year overall survival (79% vs 89%; P = 0.607) and 5-year disease free survival (52% vs 53%; P = 0.657) rates were not significantly different between the

Table 1. Comparison of perioperative outcomes between patients who underwent OLR and LLR for lesions located in PS segments (for Abstract no P-079)

	OLR group (n=124)	LLR group (n=149)	P value
Age	60±11	58±11	0.095
Gender			0.167
Male	104 (83.9)	115 (77.2)	
Female	22 (16.4)	34 (22.8)	
Tumor size (cm)	5.9±4.2	3.2±1.8	0.000
Operation time (min)	311.5±105.7	349.5±184.6	0.052
Blood loss (ml)	1244±1774	1305±2478	0.839
Transfusion, n (%)	31 (25)	44 (29.5)	0.427
Operation type, n (%)			0.000
Turnorectomy	12 (9.7)	45 (30.2)	
Mono/bi-Segmentectomy	11 (8.9)	36 (24.2)	
Caudate lobectomy	4 (3.2)	8 (5.4)	
Left hemihepatectomy	16 (12.9)	4 (2.7)	
Right anterior sectionectomy	8 (6.5)	8 (5.4)	
Right posterior sectionectomy	12 (9.7)	22 (14.8)	
Right hepatectomy	35 (28.2)	22 (14.8)	
Extended right hepatectomy	10 (8.1)	2 (1.3)	
Central bisectionectomy	17 (12.9)	2 (1.3)	
Type of resection			0.000
Anatomical	101 (81%)	81 (54%)	
Non-anatomical	23 (19%)	68 (46%)	
Cirrhosis, n (%)	81 (65.3)	99 (66.4)	0.846
Resection margin (cm)	0.99±1.25	1.15±1.59	0.244
Complication, n (%)	50 (40.3)	28 (18.8)	0.000
Hospital stay (days)	18±22	10±10	0.000

OLR, open liver resection; LLR, laparoscopic liver resection.

groups. The proportion of LLR increased (36% vs 69%, $P < 0.001$). Compared to OLR group, complication rate (40.3% vs 18.8%; $P < 0.001$) and hospital stay (18 days vs 10 days; $P < 0.001$) were significantly lower in LLR group. **Conclusion:** The complexity of LLR for HCC in PS segments has been gradually overcoming by the adaptation of advanced techniques.

P-080**The Safety and Efficacy of Liver Surgery for Very Elderly Patients**

Tomoki Hakozaiki¹, Tatsuya Yamazaki¹, Takahito Hirai¹, Yusuke Wada¹, Koji Nogaki¹, Kazuhiro Matsuda¹, Tomokazu Kusano¹, Tomotake Koizumi¹, Takeshi Aoki¹, Masahiko Murakami¹

¹Showa University Hospital, Department of Gastroenterological and General Surgery, Japan

Introduction: The proportion of 75 years over to the total population in Japan is 13.3%, and elderly patients who undergo surgery are also increasing. While the safety of hepato-

tectomy has improved due to the advancement of surgical technique and perioperative management, elderly people have some preoperative complications and perioperative risks. However, the reviews of hepatectomy outcome for elderly patients are inadequate. **Aim:** We evaluate surgical outcome of hepatectomy for patients over 80 years. **Method:** We examined the records of 327 patients who underwent hepatectomy (partial hepatectomy, segmentectomy and lobectomy) in January 2007 to November 2017. We divided patients into three groups based on the age, over 80 years (Group A, n = 38) and 65 years old and under 80 years (Group B, n = 152), less than 65 years old (Group C, n = 137), patient characteristics and surgical results were investigated. **Results:** The average age of Group A was 83 (80–89) years old. Indications of surgery was hepatocellular carcinoma (n = 21). Hepatectomy included 1 right hemihepatectomy, 12 partial hepatectomies, 5 subsegmentectomies and 3 segmentectomies. Laparoscopic hepatectomy was performed in 8 cases (38.1%). The average operation time was 205 (85–620) minutes, the blood loss was 228.5 (5–815) g. There was no significant difference between three groups. Only one patient obtained postoperative complications (Clavien-Dindo classification Grade 3) in Group A. No postoperative death was recorded

during the hospitalization of the patients. The average length of hospital stay was 16.5 (6–39) days. **Conclusion:** Hepatectomy can be tolerated for very elderly patients under careful patient selection. Laparoscopic hepatectomy may contribute to reduction of postoperative complications.

P-081

Long-Term Survival of Laparoscopic Hepatectomy for Hepatocellular Carcinoma: A Single-Center Experience

Akihisa Nagatsu¹, Toshiya Kamiyama¹, Yoh Asahi¹, Shingo Shimada¹, Tatsuya Orimo¹, Hirofumi Kamachi¹, Akinobu Taketomi¹

¹Gastroenterological surgery 1, Hokkaido University, Japan

Background: Laparoscopic liver resection is rapidly spreading due to its minimal invasiveness. In recent years, there is a report that laparoscopic hepatectomy is superior to open hepatectomy in overall survival with propensity score matching in patients with hepatocellular carcinoma. Although the reason is not clear, it is a recent trend that laparoscopic liver resection can be replaced with open liver resection.

Patients and Methods: 637 patients who underwent hepatectomy for hepatocellular carcinoma with no residual tumors in our department from January 2001 to March 2019. They divided into the group that performed laparoscopic hepatectomy (n = 74) and the group that performed open liver resection (n = 563). The patient background, oncology factors, overall survival time and recurrence-free survival time were compared. **Results:** There were more women in the laparo-

scopic group, higher PIVKA2, shorter surgery time, smaller maximum diameter with less bleeding, and one more in number. There is no significant difference on overall survival (73.6%, 83.9%, 5 years). However, there is significant difference on disease free survival (30.4%, 42.8%, 5 years). The prognostic factors on overall survival were examined by multivariate analysis. The use of laparoscopy was not independent prognostic factor. The differentiation, number of resected segments, progression, tumor diameter, ICG test, platelets counts, operation time, and tumor number were independent prognostic factors. **Discussion:** In this study, the laparoscopic group showed no significant difference in overall survival compared with the open group but was significantly better in recurrence-free survival. However, the laparoscopic group included more cases with relatively low progress compared to open group depending on the indication for surgery. The use of laparoscope itself was not an independent prognostic factor. **Conclusions:** Laparoscopic liver resection for hepatocellular carcinoma is considered to be replaceable although there is no advantage over open liver resection.

P-082

Failure to Achieve sequential Hepatectomy for Hepatocellular Carcinoma after Preoperative Portal Vein Embolization

Yosuke Nakao¹, Katsunori Imai¹, Yo-ichi Yamashita¹, Rumi Itoyama¹, Toshihiko Yusa¹, Tatsunori Miyata¹, Shigeki Nakagawa¹, Hirohisa Okabe¹, Hiromitsu Hayashi¹, Akira Chikamoto¹, Takatoshi Ishiko¹, Hideo Baba¹

¹Department of Gastroenterological Surgery, Kumamoto University, Japan

Background: Portal vein embolization has been widely used worldwide to induce hypertrophy of the future liver remnant and reduce the risk of hepatic insufficiency and death after major hepatectomy. However, some patients who were scheduled to perform PVE followed by hepatectomy for hepatocellular carcinoma could not undergo subsequent hepatectomy. **Methods:** From a total of 148 patients who were planned to perform portal vein embolization followed by hepatectomy between 2000 and 2017, 93 patients with hepatocellular carcinoma were enrolled in this study. We evaluated their long-term oncological outcomes and identified predictive factors related to the failure of planned strategy. **Results:** Among the 93 patients, 29 patients (31%) failed to achieve sequential hepatectomy. The reasons of failure were as follow; insufficient future liver remnant volume (n = 11), disease progression (n = 10), poor liver function (n = 6) and poor general condition (n = 2). Their overall survival was significantly worse than that of those who achieved to sequential hepatectomy (p = 0.009). Multivariate analyses revealed that indocyanine green retention rate at 15 min >15% (Relative

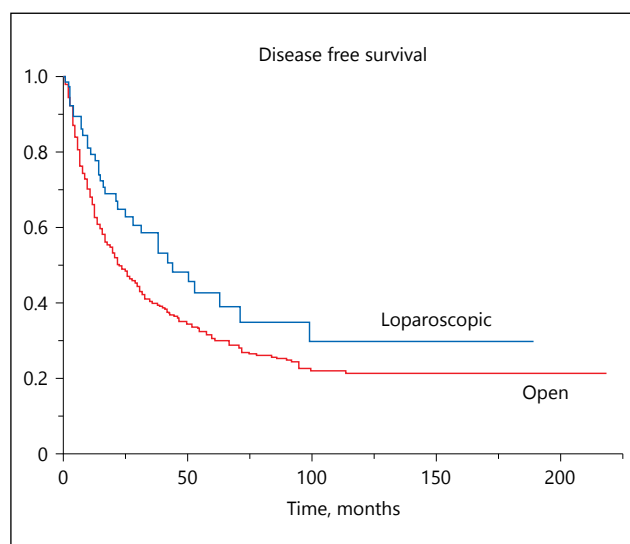


Fig. 1. (for Abstract no P-081).

risk 8.37, $p = 0.001$) and platelet count $<10 \times 10^4/\mu\text{l}$ (Relative risk 7.09, $p = 0.01$) were independent predictive factors for failure of this planned strategy. For patients not presenting any factors, the probability of failure was 2.8%. The addition of one factor increased the risk to 18.5% (indocyanine green retention rate at 15 min $>15\%$) and 23.7% (platelet count $<10 \times 10^4/\mu\text{l}$), respectively. The addition of both factors increased the risk to 70.8%. **Conclusions:** The prediction for failure of planned hepatectomy for hepatocellular carcinoma after portal vein embolization could contribute to better selecting patients in this strategy. The cirrhotic patients with impaired liver function may be contraindication to this strategy.

P-083**Comparison of Single Port Laparoscopic and Open Surgery in Minor Hepatectomy for Hepatocellular Carcinoma**Tae Yun Lee¹, Y.K You¹, H.J Choi¹¹Seoul St. Mary's hospital, Korea

Introduction: Since the introduction of laparoscopic surgery, laparoscopic surgery has been attempted in various fields. However, in liver resection, because of the technically difficult, only a small number of retrospective studies have been reported for single port laparoscopic procedures. The purpose of this study was to investigate the surgical safety and outcome of single port laparoscopic procedure in minor hepatectomy for HCC. **Material and Method:** We retrospectively reviewed the medical records of 199 patients who underwent minor hepatectomy for HCC from January 2009 and April 2018. We divided the surgical technique into two group ; single port laparoscopic hepatectomy (SPLH) and open hepatectomy (OH). A minor resection is one in which 2 or fewer Couinaud segments are removed. The same

criteria as laparoscopic or open surgery were applied. **Result:** Of the 199 patients, 73 patients underwent SPLH and 126 patients underwent OH. The characteristics of patient between two groups were almost the same. There was statistically significant decrease in operation time, blood loss, RBC transfusion, hospitalized day, enteral feeding day and post operative complication. There was no difference in recurrence rate between the two groups ($p = 0.117$). The graphs on the overall survival and disease free survival curve seemed to be different, however, there was no statistically significant difference ($p = 0.057$ and $p = 0.056$) respectively. **Discussion:** In a previous study, we showed that multi-port and single port hepatectomy were not different in terms of surgical outcome. In this paper, SPLH and OH in a minor hepatectomy were safe and feasible for survival and recurrence, showing superiority in operation time, blood loss, enteral feeding day, hospital stay, and postoperative complications.

P-084**Simulation of Remnant Liver Ischemia by Three-Dimensional Visualization Technology Based on Pre-Operative CT Scan**Xiao-Long Li¹, Xiao-Dong Zhu¹, Hui-Chuan Sun¹¹Fudan University, China

Background: To evaluate the assessment of post-hepatectomy remnant liver ischemia (RLI) by three-dimensional visualization technology (3DVT) based on pre-operative computed tomography (CT) scan. **Methods:** We retrospectively analyzed patients who received lobectomy or segmentectomy and took contrast-enhanced CT scans before and 1-week after resection in our department from June 2017 to December 2018. We simulated and estimated the occurrence

Table 1. (for Abstract no P-083)

	SILS (n = 73)	OLR (n = 126)	p value
Op time	101.75±48.51	162.09±62.26	<0.001
Blood loss	307.71±471.84	584.47±659.19	0.001
RBC T/F	0.3±0.893	0.9±1.771	0.002
Disease free margin	0.8589±0.69968	0.8688±0.91288	0.937
Hospitalized day	8.82±2.983	11.07±4.279	<0.001
Enteral feeding (day)			
Post op complication	2/73 (2.7%)	14/126 (11.1%)	0.036
Pleural effusion		7	
Ascites	2	2	
Post op bleeding		2 (GI bleeding)	
Others		Remnant tumor/ ARF/pneumothorax	
Recurrence(23F u Loss)	41/71 (57.7%)	48/105 (45.7 %)	0.117
In 1 year	24	22	

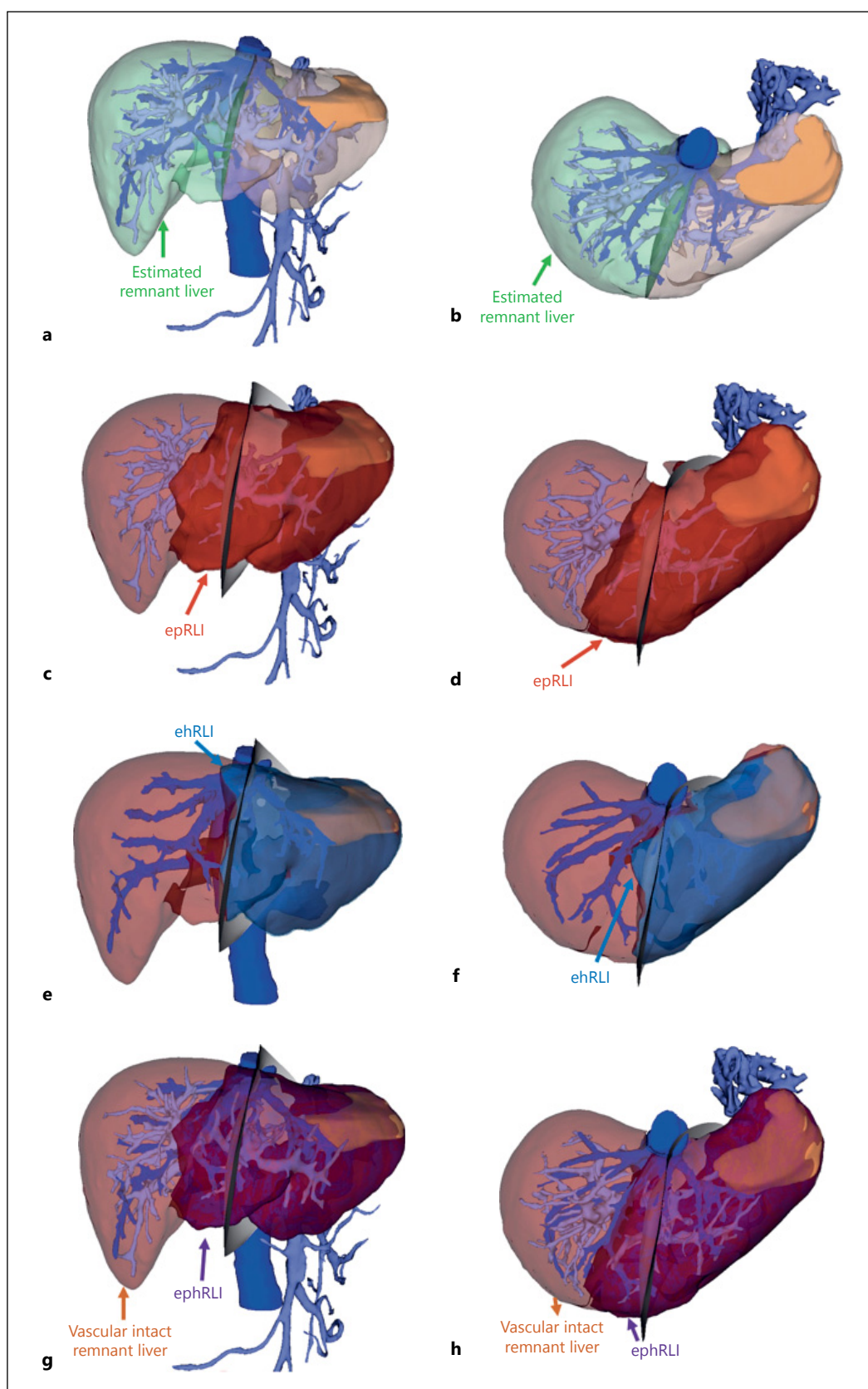


Fig. 1. (for Abstract no P-084).

of portal-vein-based RLI (epRLI), hepatic-vein-based RLI (ehRLI), portal/hepatic-vein-based RLI (ephRLI), and vascular intact-remnant liver volume (VI-RLV) after hepatectomy via 3DVT according to the pre- and post-operative CT images, blood vessels ligated in the resection, and recalled transection plane using standardized liver volume (SLV) as denominator to reduce individual variation. Then we analyzed association between the estimated RLI parameters and postoperative clinical outcomes. **Results:** A total of 79 eligible patients were analyzed. We determined that the optimal cutoff value of estimated RLI parameters in predicting actual RLI was 1.55% and subsequently classified patients into two groups. Thirty patients (38%) exhibited post-hepatectomy liver failure (PHLF), which was classified as grade A in 27 and grade B in 3 patients. Thirty-seven patients (47%) exhibited postoperative complications, including grade I in 21, grade II in 4, and grade III in 12 patients. Univariate followed by multivariate logistic regression analysis showed that epRLI/SLV >1.55% (Odds Ratio [OR], 5.0; 95% confidence interval [CI], 1.0–23.9; $P = 0.044$) were independent risk factors for PHLF and ehRLI/SLV >1.55% (OR, 25.2; 95% CI, 2.4–269.6; $P = 0.008$) were independent risk factors for grade III postoperative complications. Besides, liver stiffness (LS) >11.75 kPa and smaller VI-RLV/SLV were both independent risk factors for PHLF and grade III postoperative complications. **Conclusions:** The present study demonstrated that RLI can be predicted during the pre-operative surgical plan by 3DVT.

P-085**Is Laparoscopic Hepatectomy Suitable for Giant Hepatic Hemangioma Larger Than 10 cm in Diameter?**

Bin Jin^{1,2}, Jin Huan Yang¹, Gang Du², Binyao Shi¹, Du Kong¹, Zhengchen Jiang¹, Hao Zhang¹, Muguo Aniu¹

¹Shandong University, China, ²Qilu Hospital, China

Background: Surgical treatment of giant hepatic hemangioma larger than 10 cm in diameter often requires major laparoscopic liver resection (LLR), which is very difficult and has a high risk of bleeding. There is no consensus as to whether giant hepatic hemangioma is an indication or a contraindication for laparoscopic surgery. **Methods:** From 2011/09 to 2018/05, 58 patients with giant hepatic hemangioma larger than 10 cm underwent laparoscopic surgery. They were divided into high-difficulty (HD) group and low-difficulty (LD) group according to the operation difficulty score. The perioperative data of the two groups were analyzed and compared. **Results:** There were 30 patients in the LD group and 28 in the HD group. No differences were showed in sex, age, ASA grade, tumor size, operation time, conversion rate, intraoperative and postoperative blood transfusion rate and postoperative complications between the two groups. The amount of bleeding in the HD group was significantly higher than that in

the LD group (285.7 ± 224.0 vs 189.6 ± 157.6 ml, $p = 0.007$). The time of hepatic hilar occlusion in the HD group was longer than that in the LD group (25.4 ± 8.8 vs 20.6 ± 7.3 min, $p = 0.001$), and the rate of hepatic hilar occlusion in the HD group was also higher than that in the LD group (71.4% vs 33.3%, $p = 0.004$). The incidence of hospitalization days and discharge time in the LD group were shorter than those in the HD group (6.3 ± 1.6 vs 8.2 ± 1.4 d, $P = 0.000$; 16.4 ± 5.5 vs 21.9 ± 4.6 h, $P = 0.019$). **Conclusions:** Although there are great difficulties and risks objectively, laparoscopic treatment of giant hepatic hemangioma is safe and feasible.

Treatment: Transarterial Approach / Percutaneous Ablative Therapy / Radiation Therapy**P-086****Appraisal of Transarterial Chemoembolization Refractoriness in Patients with Hepatocellular Carcinoma**

Jonggi Choi¹, Danbi Lee¹, Ju Hyun Shim¹, Kang Mo Kim¹, Young-Suk Lim¹, Yung Sang Lee¹, Han Chu Lee¹

¹Asan Medical Center, University of Ulsan College of Medicine, Korea

Background and Aims: In real-world practice, transarterial chemoembolization (TACE) has been widely used for treating hepatocellular carcinoma (HCC) beyond, as well as within, guideline recommendations. Some guidelines defined TACE-refractoriness by consensus to encourage switching other treatment modalities. This study was to verify that two consecutive non-responses could be an optimal criterion for stopping rule for TACE. **Methods:** This study evaluated 200 patients with HCC beyond the Milan criteria initially treated with on-demand TACE. TACE response was determined by mRECIST criteria using dynamic CT or MRI. Median follow-up duration was 23.9 months. **Results:** The 200 patients consisted of 183 (91.5%) men and 17 (8.5%) women, of mean age 59.8 years. The mean size of the largest tumor was 6.8 cm, and 80 (40.0%) patients had 4 or more tumors. After the first TACE session, complete response, partial response, stable disease, and progressive disease were observed in 48 (24.0%), 87 (43.5%), 59 (29.5%), and 6 (3.0%) patients, respectively. Forty-five (22.5%) patients showed no objective response (OR) twice consecutively at any time during repeated TACE. Of these, 28 received subsequent TACE with an 10.7% of objective response rate. Patients without OR had poorer survival compared to patients achieved OR after repeated TACE. Multivariable analysis showed that the size of the

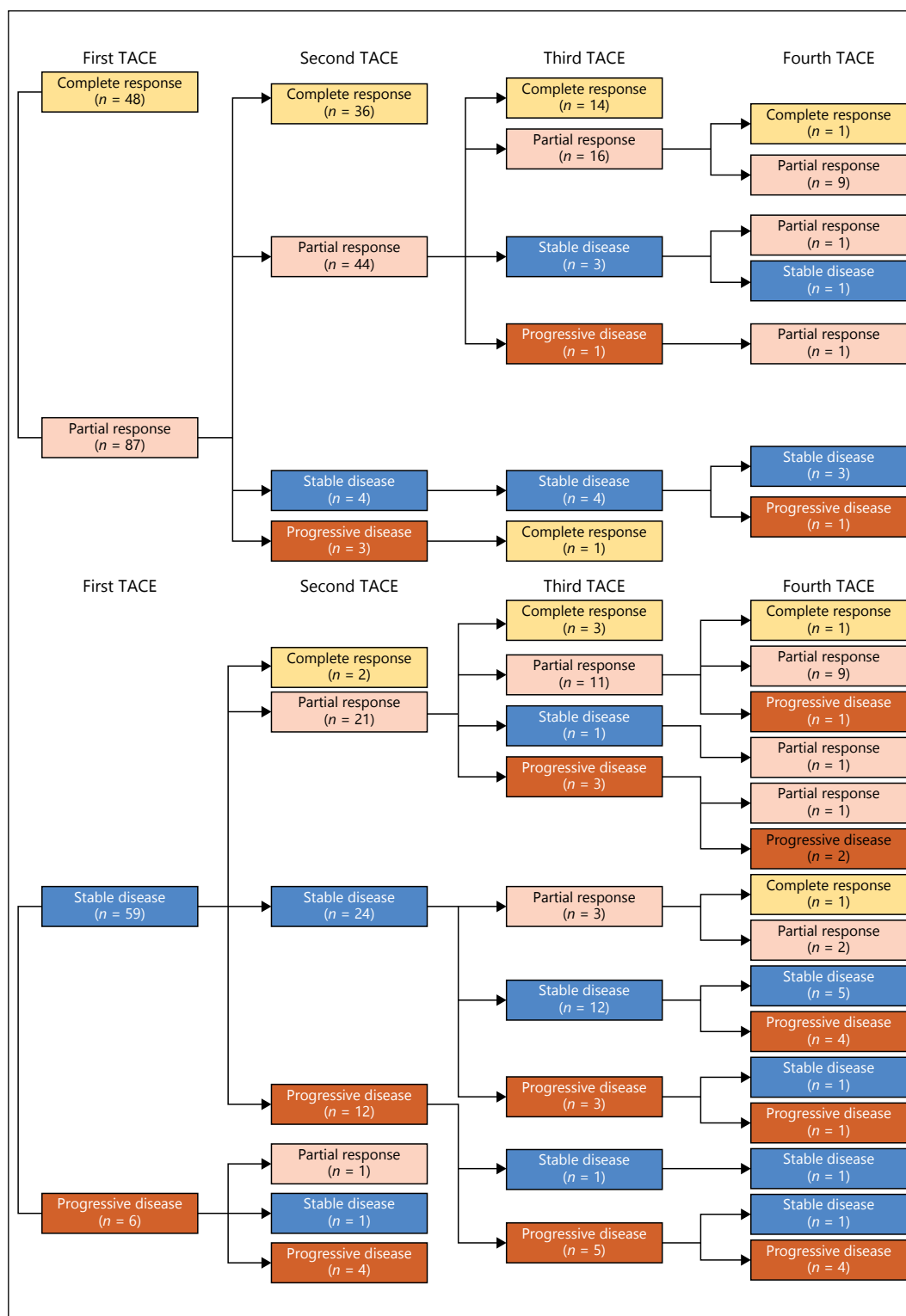


Fig. 1. (for Abstract no P-086).

largest tumor larger than 5 cm and high AFP of >200 ng/mL were significant factors associated with failure of OR twice after repeated TACE. **Conclusions:** Repeated TACE without OR twice resulted in poor response to subsequent TACE. Early transition to systemic therapy may be advocated in patients refractory to TACE.

P-087

Prognostic Value of Alpha-Fetoprotein in Patients Who Achieved Complete Response to Transarterial Chemoembolization for Hepatocellular Carcinoma

Jae Seung Lee¹, Seung Woon Paik², Kwon Yoo³, Seong Gyu Hwang⁴, Sung Won Cho⁵, Nae-Yun Heo⁶, Mong Cho⁷, Min Kyu Kang⁸, Se Young Jang⁹, Beom Kyung Kim¹, Jun Yong Park¹, Do Young Kim¹, Sang Hoon Ahn¹, Kwang-Hyub Han¹, Seung Up Kim¹

¹Yonsei University College of Medicine, Korea,

²Samsung Medical Center, Korea, ³Ewha Womans University College of Medicine, Korea, ⁴CHA Bundang Medical Center, Korea, ⁵Ajou University School of Medicine, Korea, ⁶Inje University Haeundae Paik Hospital, Korea, ⁷Pusan National University Yangsan Hospital, Korea, ⁸Yeungnam University Medical Centre, Korea, ⁹School of Medicine, Kyungpook National University, Korea

Background/Aims: The prognostic values of alpha-feto-protein (AFP) in patients with hepatocellular carcinoma (HCC) are well-known. We investigated whether AFP is prognostic in patients with HCC who achieved radiological complete response (R-CR) after TACE. **Method:** Between 2005 and 2018, 917 patients with HCC (588 treatment-naïve [TN-HCC] and 322 with recurrent HCC after curative resection [R-HCC]) who achieved R-CR after TACE (index date), based on mRECIST criteria, were recruited. “AFP response” was defined as the percentage of baseline AFP and AFP at R-CR. **Results:** The median age of patients in TN-HCC (433 male) and those in R-HCC (277 male) was 62.2 and 59.8 years, respectively. 390 (66.3%) in TN-HCC and 253 (78.6%) in R-HCC experienced recurrence. 304 (51.7%) in TN-HCC and 125 (38.8%) in R-HCC died. The median PFS in TN-HCC and R-HCC groups was 17.1 and 15.5 months, whereas the median OS was 56.4 vs. 90.4 months, respectively. In TN-HCC group, AFP at R-CR >20 ng/mL (HR = 1.349) and BCLC stage B and C (HR = 1.387) independently predicted the shorter PFS (all $P < 0.05$), whereas only multiple tumors independently predicted the shorter PFS in R-HCC group (HR = 1.892, $P < 0.001$). In TN-HCC group, baseline AFP >20 ng/mL independently predicted shorter OS (HR = 1.738), together with age >70 years (HR = 1.375), multiple tumors (HR = 1.423), prothrombin time at baseline (HR = 5.052) and shorter PFS (HR = 0.980) (all $P < 0.05$). In R-HCC group, AFP response independently predicted

Table 1. Multivariate analysis for progression-free survival after achieving CR (for Abstract no P-087)

Variables	P value	Multivariate Odds ratio (95% CI)
Total		
BCLC B/C vs. 0/A	0.025	1.298 (1.034–1.630)
Multiple tumors	0.001	1.387 (1.152–1.670)
Baseline AFP >20 ng/mL	0.597	1.055 (0.866–1.285)
AFP at CR >20 ng/mL	0.035	1.281 (1.017–1.612)
Albumin at CR	0.053	0.858 (0.735–1.002)
Naïve HCC		
BBCLC B/C vs. 0/A	0.031	1.387 (1.030–1.870)
Multiple tumors	0.430	1.105 (0.862–1.416)
Baseline AFP >20 ng/mL	0.416	1.110 (0.863–1.429)
AFP at CR >20 ng/mL	0.043	1.349 (1.010–1.802)
Albumin at CR	0.077	0.840 (0.692–1.019)
Recurrent HCC		
BBCLC B/C vs. 0/A	0.371	1.175 (0.825–1.675)
Multiple tumors	<0.001	1.892 (1.411–2.537)
Baseline AFP >20 ng/mL	0.759	1.052 (0.759–1.458)
AFP at CR >20 ng/mL	0.540	1.128 (0.768–1.656)
Albumin at CR	0.383	0.885 (0.673–1.164)

Table 2. Multivariate analysis for overall survival after achieving CR (for Abstract no P-087)

Variables	P value	Multivariate Odds ratio (95% CI)
Total		
Age >70	0.004	1.443 (1.123–1.854)
Multiple tumors	0.002	1.405 (1.137–1.737)
Baseline AFP >20 ng/mL	0.007	1.467 (1.112–1.936)
Bilirubin at CR	<0.001	1.401 (1.220–1.608)
AFP at CR >20 ng/mL	0.666	0.940 (0.709–1.246)
Progression free survival	<0.001	0.977 (0.971–0.982)
Naïve HCC		
Age >70	0.036	1.375 (1.021–1.853)
Multiple tumors	0.006	1.423 (1.10–1.829)
Baseline INR	0.029	5.052 (1.15–21.715)
Baseline AFP >20 ng/mL	0.001	1.738 (1.249–2.419)
AFP at CR >20 ng/mL	0.113	0.764 (0.548–1.006)
Progression free survival	<0.001	0.980 (0.974–0.986)
Recurrent HCC		
Multiple tumors	0.082	1.436 (0.956–2.157)
BBCLC B/C vs. 0/A	0.439	1.214 (0.743–1.985)
Baseline bilirubin	<0.001	1.420 (1.180–1.709)
AFP at CR >20 ng/mL	0.115	1.408 (0.921–2.154)
AFP response (%)	0.044	1.003 (1.000–1.005)
Progression free survival	<0.001	0.963 (0.950–0.977)

shorter OS (HR = 1.003), together with higher bilirubin level (HR = 1.450) and shorter PFS (HR = 0.963) (all $P < 0.05$).

Conclusion: AFP at R-CR and AFP response were independently predictive of recurrence and mortality in TN-HCC and R-HCC, respectively. AFP should be used for more detailed risk stratification even after achieving R-CR after TACE.

P-088

Prognostic Value of Des-γ-Carboxy Prothrombin Responses in Recurrent Hepatocellular Carcinoma Patients Treated with Transarterial Chemoembolization

Yi Chen¹, Xin Xu¹, Lan Zhang¹, Zhenggang Ren¹, Yanhong Wang¹

¹Zhongshan Hospital, Fudan University, China

Objective: Des-gamma-carboxy prothrombin (DCP) has played an important role in diagnosis of hepatocellular carcinoma (HCC). However, its ability on the prediction for the response of treatment is still doubtful. We evaluated the relationship between the change of DCP values and tumor responses in HCC patients undergoing trans-arterial chemoembolization (TACE). **Materials and Methods:** From June 2018 to Sep 2018, a total of 68 recurrent HCC patients underwent TACE at Zhongshan Hospital, Fudan University were enrolled. Serum levels of AFP and DCP were measured using the chemiluminescent assay and clinical features were examined for all the patients at baseline and at one month after the procedure. DCP response was defined as a reduction of more than 50% from the baseline level one month after TACE. **Results:** All patients received a classical TACE procedure, systemic therapy with Sorafenib was added in 24 patients (35.3%). DCP and AFP were 91.2%(62/68) and 67.6% (46/68) positive, respectively. AFP value significantly decreased at one month (median value 2706.3 vs. 1614.7 ng/mL, $p = 0.045$), and the same significant decrease was noted for DCP values (median value 4530.8 vs. 3144.7 mAU/mL, $p = 0.023$). DCP response was identified in 30 (44.1%) patients after TACE. Multivariate analyses showed that baseline DCP, AFP and tumor size were predictors of PFS (all $P < 0.05$). However, DCP response did not influence PFS ($P > 0.05$). Correlative analyses showed that tumor size, tumor number, and BCLC stage were associated with baseline DCP level. **Conclusion:** Baseline DCP level may lead to poor prognosis, though DCP response is not significant predictor of tumor response after TACE for HCC patients.

P-089

Albumin-Bilirubin (ALBI) and Platelet-Albumin-Bilirubin (PALBI) Grade for Predicting of Three Months Survival in HCC Patients Receiving Transarterial Chemoembolization

Ummi Maimunah^{1,2}, Annisa Z. Mufida^{2,3}, Iswan A. Nusi^{1,2}, Herry Purbayu^{1,2}, Titong Sugihartono^{1,2}, Irawati H. Kikuko³, Poernomo B. Setiawan^{1,2}

¹Division of Gastroentero-hepatology, Internal Medicine Department, Dr. Soetemo General Hospital, Indonesia, ²Internal Medicine Department, Dr. Soetemo General Hospital, Surabaya, Indonesia, ³Faculty of Medicine Airlangga University Surabaya,, Indonesia

Background: ALBI and PALBI grading are simple and objective prognostic tools to predict survival in Hepatocellular Carcinoma (HCC) patients receiving Transarterial Chemoembolization (TACE). It is expected as more accurate predicting both grading compared with Child-Pugh (CP). **Methods:** We retrospectively reviewed 113 HCC patients receiving TACE from 2013 to 2017 at dr Soetomo general hospital Surabaya, Indonesia. ALBI and PALBI were classified into three groups and analyzed their correlation with CP grading. Mean of three months survival (mean 3MS) outcomes were measured using Kaplan-Meier method. **Results:** Patients were classified by ALBI grading, Group 1 was 13.3%, 2 was 80.5% and 3 was 6.2%. Mean 3MS for group 1 was 10.8 weeks, 2 was 9.4 weeks, 3 was 9.8 weeks. PALBI grading, Group 1 was 27.4%, 2 was 42.5% and 3 was 52.2%. Mean 3MS for group 1 was 10 weeks, 2 was 10.2 weeks, 3 was 9.2 weeks. CP grading, Group A was 27.4%, B was 72.6%. CP was stratified on ALBI and PALBI. There were not significant [$p > 0.05$]. **Conclusions:** There is no significant differences in ALBI, PALBI in CP grading. We need further overall survival studies using both to achieve more accurate predicting survival.

P-090

Strengthening Intraoperative Hemodynamic Monitoring for Nursing Patients with Liver Rupture of Liver Cancer

YiLing Cao¹

¹Zhongshan Hospital Fudan University, China

Objective: Liver rupture is associated with hemorrhagic shock, and patients with hemodynamic instability have a higher mortality rate. Therefore, this study improved treatment efficiency by enhancing hemodynamic monitoring in patients with hepatic rupture. **Methods:** A total of 54 patients with liver rupture of liver cancer were treated in this study. After the end of the emergency consultation, the respi-

ratory tract was quickly opened to keep the breathing open, venous access was established to keep the infusion smooth, and the patient's hemodynamics were restored and corrected as soon as possible. Diagnostic abdominal puncture assessment, CT examination, blood routine examination, and hemodynamics were performed before surgery. Shortening preoperative preparation time, establishing multiple infusion channels, and using a central venous catheter combined with a peripheral superficial venous indwelling needle were processed to improve surgical tolerance. Timely organization of emergency TACE, intraoperative monitoring of ECG, oxygen saturation, hemodynamics, and blood routine was undertaken. **Results:** All 54 patients underwent emergency TACE. Among of them, one patient had severe hemorrhage after TACE and died 48 hours after surgery. The remaining patients were discharged from the hospital. **Conclusion:** Strengthening the monitoring of hemodynamic parameters in patients with liver rupture of liver cancer could improve the efficiency of preoperative preparation, strive for surgery time, make sure the operation goes smoothly, improve the success rate of surgery and improve the prognosis of patients.

P-091

Survival Comparison of Patients with Hepatocellular Carcinoma undergoing Single vs. High-Risk Re-Transarterial Chemoembolization: Which One Is Better?

Poernomo B. Setiawan¹, Frida L. Pitoyo¹,
Ummi M. Maimunah¹

¹Dr Soetomo Hospital Airlangga University Faculty of Medicine, Indonesia

Background: Transarterial chemoembolization (TACE) result for unresectable hepatocellular carcinoma (HCC) patients are limited by several conditions. High ART score is to be claimed as one of worse parameter in re TACE patients. We want to compare the overall survival (OS) underwent single TACE vs. high-risk re-TACE patients. **Methods:** A retrospective study of 72 HCC patients who were treated either with single (59 pts) or (13 pts) high risk re TACE in Dr. Soetomo Hospital (Surabaya, Indonesia). High risk patients if they had re TACE despite having a high-ART score (≥ 2.5 point, calculated 1 day before re TACE). OS was defined as length of time from the date of first TACE session to the patient death. We used Kaplan Meier for survival and log rank for comparison analysis. **Results:** Single treatment patients have younger median of age (51 vs. 57 years old), larger size tumor (11.3 vs. 9.27 cm), and poorer liver function (72.9% Child Pugh B vs. 92.3% Child Pugh A) than those re TACE patients respectively. There was no difference in etiology, tumor number, AFP levels, and objective responses. Median OS of high-risk re- TACE patients were significantly better than single TACE patients (median OS: 11.9 vs. 4 months, $p = 0.044$).

Conclusions: Re TACE sessions provide superior survival benefits compare to a single session even if performed in high-risk patients.

P-092

Conventional TACE could be Ineffective for Tumor Necrosis in patients of HCC with Micro-Vascular Invasion (MVI); MVI Could be a Strong Indicator for Recurrence within 2-year after Curative Hepatic Resection

Joon Ho Jeong¹, KWANG IL SEO¹, Byung Chul Yun¹,
Jung Gu Park¹, Sang Uk Lee¹, Byung Hoon Han¹,
Eun Taek Park¹, Jin Wook Lee¹, Kyung Seung Oh¹

¹Kosin University, College of Medicine, Korea

Aim: This study aims to investigate the factor that could affect tumor necrosis of HCC on TACE; we also conducted study to look into the factor associated with early recurrence of HCC within Milan Criteria after curative hepatectomy. **Method:** Retrospectively, 60 patients who had only once preoperative TACE in a single university hospital were selected. The tumor necrosis after TACE was analyzed with the pathology report of surgical specimen. **Results:** In enrolled 60 patients, the mean of age was 61.9 (± 8.38), the mean of tumor size was 2.79 (± 1.39 cm). The the rates of HBsAg positivity and anti-HCV positivity were 71.7% and 11.7% respectively; the number of MVI-positive was 13 (21.7%). In multi-variable logistic regression analysis, MVI only could give influence to the extent of tumor necrosis. ($p = 0.030$). The mean of age in the MVI-positive and MVI-negative group were 62.92 (± 9.02), 61.62 (± 8.28), ($p = 0.644$); the mean of tumor size in the two group were 3.85 (± 2.01), 2.50 (± 1.01), ($p = 0.054$); the mean of AFP serum level in each group was 321.4 (± 426.9), 287.64 (± 1041.06), ($p = 0.862$) respectively. The extent of tumor necrosis in the MVI-positive and MVI negative group were 34.08% (± 38.87), 80.26% (± 35.82) ($p = 0.006$) respectively. The mean of observation-period was 2472 days (± 201.81); the recurrence free survival rate in MVI positive & negative group were 31.8% and 71.4%, respectively ($p = 0.0001$). In cox-regression analysis, MVI and PT (INR) statistically gave influence to the recurrence within two-year ($p = 0.001$ and 0.004). **Conclusions:** Conventional TACE could not be a best option for the treatment of HCC with MVI; additionally, two-year recurrence rate was higher in MVI-positive group than MVI-negative group after curative hepatectomy.

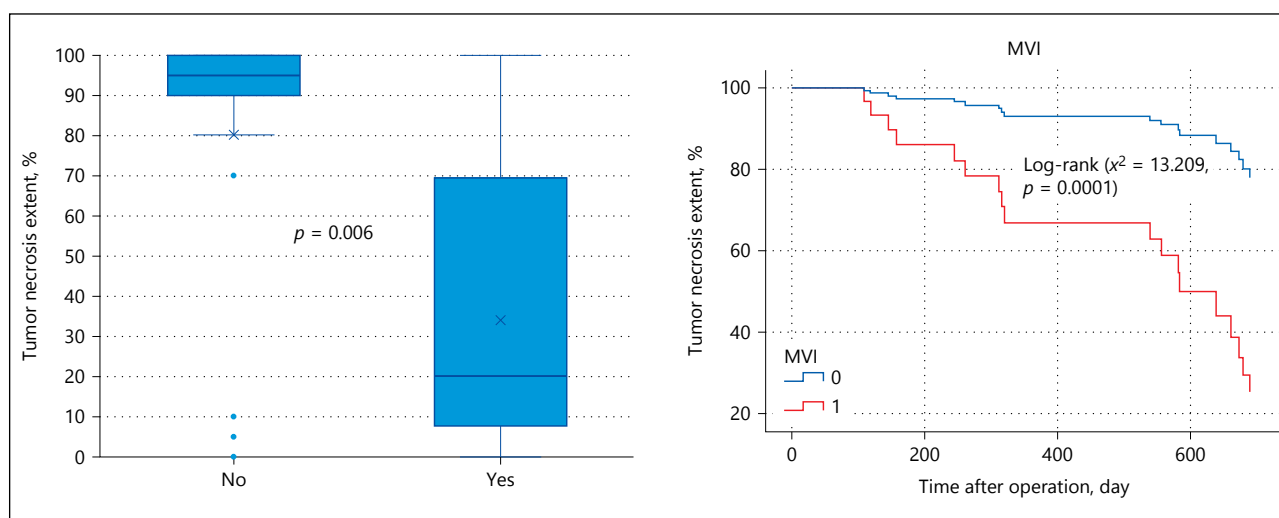


Fig. 1. (for Abstract no P-092).

P-093

Aortoceliac Angle in Percutaneous Implantation of Port-Catheter System for Hepatic Arterial Infusion Chemotherapy: Comparison of Subclavian vs Femoral Approach

Su Ho Kim¹, Ho Jong Chun¹, Si Hyun Bae¹,
Seung Kew Yoon², Pil Soo Sung¹, Jeong Won Jang²

¹Eunpyeong St. Mary's hospital, Korea, ²Seoul St. Mary's hospital, Korea

Objective: The purpose of this study was to retrospectively compare the aortoceliac angle of patients with advanced HCC who underwent implantation of port-catheter system for hepatic arterial infusion chemotherapy (HAIC) via the femoral artery and via the left subclavian artery after unsuccessful implantation by the femoral artery approach. **Method:** Between Jan 2008 and Nov 2018, in 16 patients port-catheter systems were implanted via left subclavian artery, after unsuccessful attempts of implantation via common femoral artery due to failure of catheter tip fixation in the gastroduodenal artery. Of 385 patients who underwent successful implantation of port-catheter system via common femoral artery during the same period, 32 patients were randomly selected with commercial software (Excel 2013, Microsoft, USA). The aortoceliac angles and ostial celiac trunk stenosis of both groups were measured on multiplanar reconstruction image of computed tomography or magnetic resonance (Aquarius iNtuition Viewer 4.4, Terarecon, USA). Aortoceliac angle, ostial celiac trunk stenosis, sex and age of both groups were analyzed using commercial software (IMB SPSS Statistics 24, IBM, USA). **Result:** The average aortoceliac angles were significantly different between the two groups (subclavian group; 20.3 ± 11.9 degrees, femoral group; 61.8 ± 18.7 degrees,

$p < 0.001$). Ostial celiac trunk stenosis (subclavian group = 1, femoral group = 2, $p = 1.000$), the distribution of sex (subclavian group M : F = 11 : 5, femoral group M : F = 27 : 5, $p = 0.267$) and age (subclavian group 55.6 ± 13.0 years, femoral group 58.7 ± 7.5 years, $p = 0.983$) of two groups were not significantly different. **Conclusion:** For patients with an acute aortoceliac angle undergoing implantation of port-catheter system for HAIC, left subclavian artery approach should be preferentially considered for stable fixation of the catheter tip in the gastroduodenal artery.

P-094

Dose Escalation in Radiotherapy for Incomplete Transarterial Chemoembolization of Hepatocellular Carcinoma

Hwa Kyung Byun¹, Hyun Ju Kim², Do Young Kim¹,
Kwang-Hyub Han¹, Jinsil Seong¹

¹Yonsei Cancer Center, Yonsei University College of Medicine, Korea, ²Gachon University Gil Medical Center, Korea

Purpose: To investigate efficacy of radiation dose escalation in patients with hepatocellular carcinoma (HCC) after incomplete transarterial chemoembolization (TACE). **Methods:** This study evaluated retrospective data of 323 HCC patients who received radiotherapy after incomplete TACE during 2001–2016. Radiation dose in biologically effective dose (BED) ($a/b = 10$) was categorized as less than 72 Gy (261 patients) and more than 72 Gy (62 patients). Simultaneous integrated boost-intensity modulated radiation therapy (SIB-IMRT) was significantly more used in high-dose group (64.5% vs. 12.9%; P -value of less than 0.001). Local failure-free rate (LFFR), progression-free rate (PFR), and toxicities were

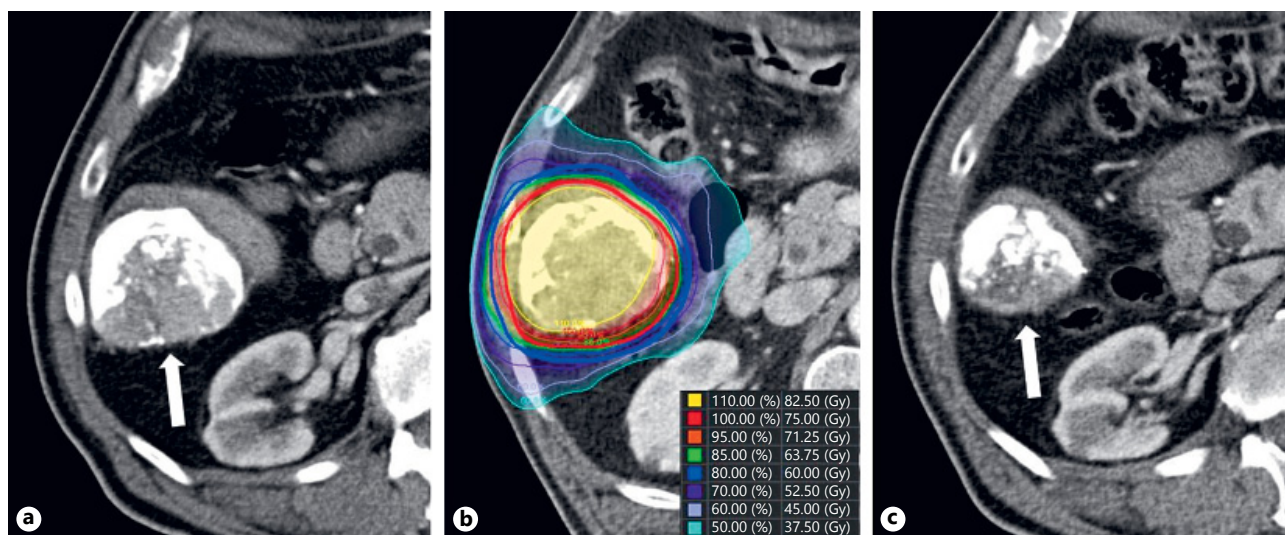


Fig. 1. (for Abstract no P-094).

compared between two groups. Additionally, propensity score matching was performed. **Results:** Median follow-up time for patients who were alive at time of analysis was 47 months (range, 18–189 months). Median overall survival after radiotherapy was 14 months. In multivariate analysis, BED more than 72 Gy was an independent predictor of favorable LFFR (hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.14–0.72; $P=0.006$) and PFR (HR, 0.67; 95% CI, 0.45–0.98; $P=.04$). In propensity score-matched cohort (62 pairs), 1-year LFFR (94% vs. 81%; $P=.002$) and 1-year PFR (49% vs. 42%; $P=.01$) were significantly higher in high-dose group. Treatment-related toxicity in high-dose group, which involved radiation-induced liver disease (5 patients) and gastrointestinal bleeding (2 patients), was comparable to that of low-dose group. **Conclusion:** Radiation dose with BED more than 72 Gy improved LFFR and PFR without increasing toxicity. In radiotherapy for incomplete TACE of HCC, dose escalation using SIB-IMRT needs active consideration to improve oncologic outcome.

P-095

Phase II Clinical Trial of Stereotactic Body Radiation Therapy for Small (≤ 5 cm) Hepatocellular Carcinoma not Amenable to Curative Treatment

Sang Min Yoon¹, So Yeon Kim², Young-Suk Lim³, Kang Mo Kim³, Ju Hyun Shim³, Danbi Lee³, Jihyun An⁴, Jinhong Jung¹, Jong Hoon Kim¹, Han Chu Lee³

¹Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea,

²Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Korea,

³Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Korea,

⁴Department of Gastroenterology, Hanyang University Guri Hospital, Korea

Background: With recent technological advances in radiation therapy, stereotactic body radiation therapy (SBRT) is regarded as an alternative local ablative treatment in hepatocellular carcinoma (HCC) that is not suitable for hepatic resection or local ablative therapy. The purpose of this prospective study was to evaluate the long-term efficacy of SBRT for small (≤ 5 cm) HCC. **Methods:** Between 2013 and 2016, 50 patients with HCC were enrolled in this phase 2, single-arm, clinical trial at an academic tertiary care center. Planned SBRT dose was 45 Gy with the fraction size of 15-Gy over 3 consecutive days. The primary endpoint was 2-year local tumor control. Radiologic response was assessed by independent review according to both Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) and modified RECIST. **Results:** Patients were 41 to 74 years of age, and 80% were male. All patients had Child-Pugh class A hepatic function before SBRT. The median follow-up period of all patients was

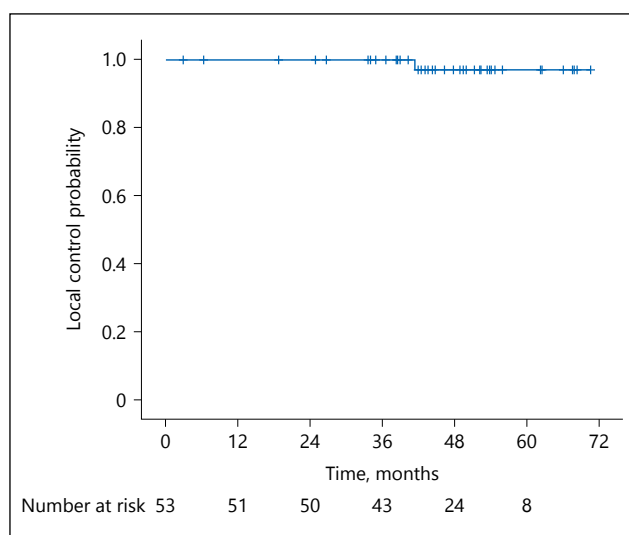


Fig. 1. (for Abstract no P-095).

47.8 months (range, 2.9–70.6), and the median tumor size was 1.3 cm (interquartile range, 1.0–1.7). The 2- and 5-year local control rates were 100% and 97.1%, respectively. The 5-year overall survival rate was 77.6%. A radiologic response was achieved in 44 (83%) lesions according to RECIST and in 49 (92.4%) according to modified RECIST at 6 months after SBRT. Any grade ≥ 3 acute or late adverse events were not observed in all patients. Two (4%) patients experienced elevation in the Child-Pugh score to ≥ 2 . **Conclusion:** SBRT was an excellent ablative treatment with acceptable toxicities

for patients with small HCC. SBRT can be a good treatment option for HCC in both curative and salvage settings that is unsuitable for curative treatment.

P-096

Prognostic Performance of Inflammation-Based Prognostic Scores in Patients with Hepatocellular Carcinoma Treated with Stereotactic Ablative Radiotherapy

Cheng-Hsiang Lo¹, Wen-Yen Huang^{1,2}, Po-Chien Shen¹, Chih-Weim Hsiang³, Chun-Shu Lin¹, Wei-Chou Chang³, Jen-Fu Yang¹, Yang-Hong Dai¹

¹Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taiwan, ²Institute of Clinical Medicine, National Yang-Ming University, Taiwan, ³Department of Radiology, Tri-Service General Hospital, National Defense Medical Center, Taiwan

Background: Several inflammation-based prognostic scores, including neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), prognostic nutritional index (PNI), and systemic immune-inflammation index (SIS) are proposed as predictive of survival in patients with hepatocellular carcinoma (HCC). This study aimed to evaluate the prognostic performance of these scores in patients with HCC treated with stereotactic ablative radiotherapy (SABR). **Methods and Materials:** This retrospective study evaluated the patients

Table 1. Multivariable analysis of prognostic factors on overall survival in different inflammation-based prognostic factor models (for Abstract no P-096)

	NLR		PLR		PNI		SIS	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total tumor volume, cc								
≥100 vs. <100	1.31 (0.89–1.94)	0.175	1.40 (0.95–2.07)	0.085	1.42 (0.96–2.08)	0.076	1.43 (0.96–2.14)	0.076
Tumor number								
multiple vs. solitary	2.34 (1.52–3.62)	<0.001	2.15 (1.40–3.31)	<0.001	2.06 (1.34–3.17)	0.001	2.13 (1.38–3.26)	0.001
Macrovascular invasion	1.51 (0.99–2.30)	0.055	1.52 (1.00–2.33)	0.053	1.53 (1.01–2.33)	0.048	1.55 (1.01–2.38)	0.043
Extrahepatic spread	2.65 (1.55–4.53)	<0.001	2.52 (1.44–4.42)	0.001	2.65 (1.55–4.53)	<0.001	2.68 (1.55–4.64)	<0.001
Performance status								
≥2 vs. 0–1	1.19 (0.69–2.03)	0.535	1.19 (0.70–2.04)	0.526	1.23 (0.72–2.08)	0.452	1.23 (0.72–2.11)	0.450
AFP level								
≥400 vs. <400	1.38 (0.92–2.06)	0.120	1.44 (0.97–2.15)	0.074	1.43 (0.96–2.13)	0.081	1.47 (0.98–2.22)	0.065
CTP A vs. B	1.57 (1.03–2.39)	0.023	1.68 (1.09–2.60)	0.019	1.46 (0.91–2.33)	0.115	1.62 (1.05–2.50)	0.030
NLR ≥5 vs. <5	2.33 (1.37–3.97)	0.002	–	–	–	–	–	–
PLR ≥150 vs. <150	–	–	1.18 (0.75–1.86)	0.465	–	–	–	–
PNI <45 vs. ≥45.1	–	–	–	–	1.25 (0.80–1.95)	0.330	–	–
SIS ≥330 vs. <330	–	–	–	–	–	–	0.99 (0.64–1.54)	0.955

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α -fetoprotein; CTP, Child-Tw-cotte-Pugh liver function scale; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PNI, prognostic nutritional index; SIS, systemic immune-inflammation index

with HCC treated with SABR between December 2007 and August 2018. We collected pretreatment NLR, PLR, PNI and SIS values and compared their prognostic performance using the area under the receiver operating characteristics curve (AUC). Cox proportional analysis was performed to identify the variables associated with overall survival. **Results:** This study included 172 patients, of them 155 was evaluable for inflammation-based prognostic scores. The PNI had a higher AUC value at 1 year (0.673) and 2 years (0.667) in comparison with other inflammation-based prognostic scores, but not statistically significant. Multivariable analysis demonstrated that the NLR was independently associated with overall survival ($P = 0.002$), along with tumor number ($P < 0.001$), extrahepatic spread ($P < 0.001$) and Child-Turcotte-Pugh classification ($P = 0.023$). **Conclusion:** Our data suggested that the NLR is a readily available predictor of survival in patients with HCC treated with SABR. Further prospective studies for validation are warranted.

P-097**Treatment Response of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis to Radiation Therapy Utilizing Helical Tomotherapy HDA**

Michael Martin H. Malabanan¹,
Gregorio Martin I Guevarra¹

¹Asian Hospital & Medical Center Asian Cancer
Institute Radiation Oncology Unit, Philippines

Background: Patient is a 78 year old gentleman managed as a case of Advanced Multifocal Hepatocellular Carcinoma with Portal Vein Thrombosis, Status-post Radiation Therapy using Tomotherapy to the HCC Mass and and to the Portal Vein

Tumor Thrombus (PVT), status-post Transarterial Chemo-embolization (February 19, 2018 and June 19, 2018), status-post SIRT (October 25, 2017), status-post Image guided Ultrasound and CT Fluoroscopic-guided Microwave Ablation of Segment 7 and 8 Hepatic Nodules. He initially presented with loss of appetite and abdominal discomfort for one month, with ECOG Performance Status of 0. **Methods:** Patient underwent Radiation Therapy using the Tomotherapy HDA in the Philippines twice. Phase one involved the entire liver mass (1029.23 cc) with a radiation dose of 5000 cGy delivered over 25 days. Phase 2 involved irradiating the portal vein tumor thrombosis (11.81 cc) to a dose of 3000 cGy delivered over 15 days. Patient response was assessed with the use of PETCT imaging after radiation therapy. **Results:** Significant tumor reduction and resolution of thrombus was observed during PETCT imaging. Toxicities and complications encountered were minimal and were well tolerated, gastric upset but with no loss of appetite. **Conclusions:** Hepatocellular carcinoma with portal vein tumor thrombosis responds well to radiation therapy with the use of the Tomotherapy HDA machine with minimal toxicity and good treatment tolerance. Radiation therapy to HCC and PVTs have become part of the treatment option in the management of advanced Hepatocellular Carcinomas in the Philippine setting. Multidisciplinary management has become a key factor in providing a longer lifespan with good quality of life for this patient. Figure 1. Radiation isodose lines for Phase 1 and Phase 2 radiation therapy (red percent of dose prescription; Blue 70 percent of dose prescription). Notice the large decrease in liver tumor volume for phase 2.

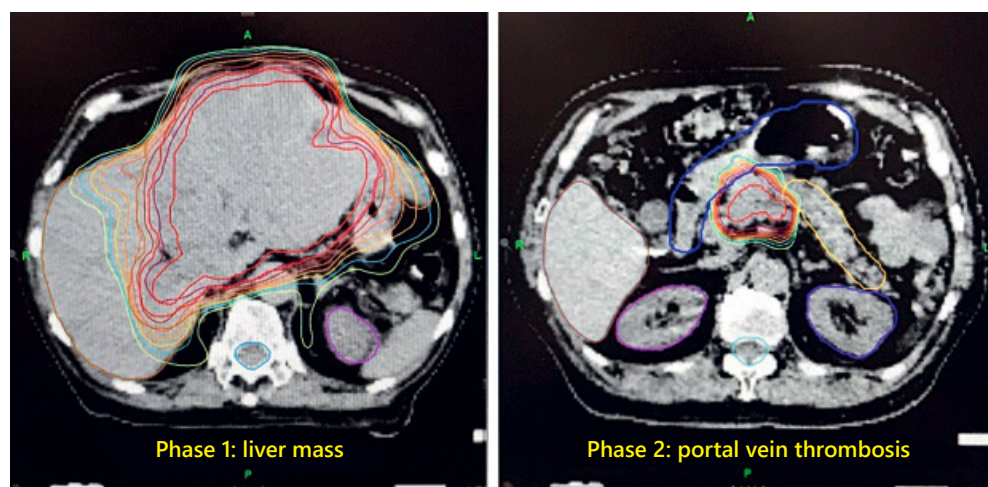


Fig. 1. (for Abstract no P-097).

P-098

**The Safety of Stereotactic Body
Radiotherapy Using Helical Tomotherapy
for Hepatocellular Carcinoma in Terms of
Intermediate Dose Spillage**

Sun Hyun Bae¹, Kwang Hwan Cho¹, Young Seok Kim²,
Sang Gyune Kim², Jae Myung Lee³, Min Hee Lee³,
Jae Hong Jung⁴, Sung Hee Lim⁵

¹Department of Radiation Oncology, Soonchunhyang
University College of Medicine, Bucheon, Korea,

²Division of Gastroenterology and Hepatology,
Department of internal medicine, Soonchunhyang
University College of Medicine, Bucheon, Korea,

³Department of Radiology, Soonchunhyang University
College of Medicine, Bucheon, Korea, ⁴Department of
General Surgery, Soonchunhyang University College of
Medicine, Bucheon, Korea, ⁵Division of Hematology-
Oncology, Department of Internal Medicine,
Soonchunhyang University College of Medicine,
Bucheon, Korea

Background/Aim: Tomotherapy is a unique rotational
intensity-modulated radiotherapy machine using a helical
dose delivery technique similar to spiral computed tomog-
raphy. Helical tomotherapy (HT) increases intermediate dose
spillage, recommended by The Radiation Therapy Oncology

Group (RTOG) to assess the rapid falloff gradient beyond the
planning target volume (PTV) into normal tissue for stereo-
tactic body radiotherapy (SBRT). We evaluated the safety of
SBRT using HT for hepatocellular carcinoma (HCC) in terms of
intermediate dose spillage. **Methods:** Between April 2014 and
September 2017, 13 HCC patients were treated with SBRT
using HT. Initial Child-Pugh class was A in 12 patients and B7
in 1 patient. SBRT dose ranged from 44 Gy to 60 Gy in 4 frac-
tions. The dose constraint of normal liver (NL) applied rNL18
Gy (reverse NL volume receiving below 18 Gy) above 700 mL
to minimize radiation-induced liver disease (RILD). Interme-
diate dose spillage was assessed by RTOG recommendation:
R50% means the ratio of the 50% prescription isodose volume
to the PTV. **Results:** All plans meet rNL18Gy above 700 mL.
Seven plans (54%) had minor deviation and 5 plans (38%)
had major deviation from R50%. With a median follow up of
26 months, the local progression-free survival, intrahepatic
progression-free survival, and overall survival rates were
89% and 46%, and 100% at 2 years, respectively. One patient
experienced classic RILD within 3 months after SBRT: PTV
was 72 mL, NLV was 1197 mL, and rNL18 Gy was 971 mL.
SBRT dose was 52 Gy and there was a minor deviation of
R50%. There was no other severe toxicity above grade 3.
Conclusions: Although SBRT using HT for HCC tends to
increase intermediate dose spillage, the treatment outcome
was comparable with other published studies of SBRT.

Author Index

- Abada, P. 127
Abada, P.B. 138
Abdullah, H. 107
Abe, M. 92
Abe, N. 158
Acosta-Rivera, M. 106
Adachi, T. 152
Ahn, H.R.I. 139
Ahn, J. 182
Ahn, K.S. 139
Ahn, S.H. 131, 132, 164, 191
Aikata, H. 90, 105
Aiyama, T. 158
Akamatsu, N. 7, 14, 69, 83, 92, 113, 160
Allen Jr. J.C. 84
Alsina, A. 107, 123
Amano, R. 101
Amarsanaa, J. 33
An, J. 195
Anderson, J. 106
Ang, A. 136
Ang, R.W.T. 84
Aniu, M. 189
Aoki, T. 49, 97, 103, 160, 185
Aosasa, S. 113
Ara, M. 180
Arai, Y. 183
Arakawa, T. 103, 160
Araki, K. 133
Ariizumi, S. 65
Arita, J. 7, 14, 83, 92, 113, 160
Asahi, Y. 89, 94, 99, 155, 186
Asaoka, Y. 149
Atmodjo, W.L. 138
- Baatarkhuu, O. 33
Baba, H. 186
Bae, S.H. 137, 167, 182, 194, 198
Bae, S.K. 83
Baek, G.O.K. 139
Bai, Y. 96
Baik, S.K. 141
Bang, K.H. 181
Berardi, G. 104
Berghoff, K. 112
Bonney, G.K. 94, 143
Bozhilov, K.K. 164
Brandi, G. 127
Breder, V. 107
Bruns, R. 112
Buhe, A. 86
- Bwa, A.H. 34
Byeon, J.H. 183
Byun, H.K. 194
Byun, J.H. 172
Byun, K.S. 176
- Cao, J. 158
Cao, Y.L. 192
Carton, I. 127
Cha, B. 146
Cha, J.H. 137
Cha, S.-W. 161
Chamadol, N. 36
Chan, A.C.Y. 15
Chan, A.C.-Y. 24
Chan, C.Y. 84
Chan, M.K.H. 110
Chan, S. 13, 183
Chan, S.L. 57, 80, 81
Chang, A.R. 167
Chang, S. 178
Chang, U.I. 152, 182
Chang, W.-C. 124, 165, 196
Chang, Y. 153, 161
Chao, Y. 134, 163, 168
Chau, G.-Y. 134
Chen, B.-B. 110
Chen, C.-H. 96
Chen, G. 132
Chen, G.-W. 88
Chen, J. 133
Chen, K.-H. 166
Chen, M. 104
Chen, M.-H. 134
Chen, R. 125, 127, 129
Chen, S.-C. 134
Chen, Y. 88, 127, 133, 192
Chen, Y.-H. 88, 116, 150
Chen, Y.-Y. 150
Cheng, A.-L. 104, 105, 107, 110, 123, 184
Cheng, C.-H. 116
Cheng, J.C.-H. 85
Cheng, P.-N. 96
Cheng, R. 127
Cheng, S.-W. 126
Cheon, G.J. 108
Cheong, J.Y. 139
Cheow, P.C. 84
Chew, V. 169
Chi, C.-T. 163
Chiang, C.L. 110
- Chikamoto, A. 186
Chin, S. 184
Chiu, J. 15
Chiu, Y.-C. 126
Cho, C. 178
Cho, C.-K. 167
Cho, E. 142
Cho, E.J. 135, 170
Cho, H.J. 139
Cho, J.Y. 184
Cho, K.H. 198
Cho, M. 171, 191
Cho, M.J. 153, 154, 157
Cho, S.B. 148
Cho, S.W. 137, 191
Cho, Y. 139
Cho, Y.D. 161
Cho, Y.K. 147
Cho, Y.Y. 170
Choe, W.H. 144
Choi, C.W. 167
Choi, G. 101
Choi, H.J. 182, 187
Choi, J. 143, 155, 189
Choi, J.-Y. 91
Choi, J.Y. 96, 137, 152, 182
Choi, M.S. 82, 176
Choi, S.H. 172
Choi, S.K. 142, 148
Choi, S.W. 152, 182
Choi, Y.H. 170
Choi, Y.I. 157
Chok, K.S.-H. 15
Choo, S.P. 13, 136, 169
Choo, S.-P. 106
Chow, P. 71, 81, 169
Chow, P.K.H. 84, 96
Chuang, P.-H. 150
Chuang, T.-T. 15
Chun, H.J. 194
Chung, A.Y.F. 84
Chung, C.-S. 166
Chung, Y.-H. 155
Cleary, S. 184
Cohen, G. 183
Costanzo, D.F. 106
Crysler, O. 106
Cui, Z.L. 138
- Dai, Y.-H. 196
Dan, Y.Y. 94, 143
Daniele, B. 105, 123

- Dao, L.T. 159
Decaens, T. 112
Do, Y.K. 96
Dong, J. 23, 151
Du, G. 189
Du, S. 132
Duda, D.G. 43
Dutcus, C. 104, 105, 107
- Egawa, H. 69
Einama, T. 113
El-Khoueiry, A.B. 106
El-Rayes, B. 106
Erinjeri, J. 183
Eun, H.S. 153, 154, 157
Eun, J.W. 139
Evans, T.R.J. 123
- Faivre, S. 112
Fan, J. 96, 167, 184
Fan, Q. 86
Fang, Y. 138
Finn, R.S. 42, 104, 105, 107, 123
Fujimori, A. 49, 97
Furukawa, H. 159
Furuse, J. 38, 96
- Galle, P. 16, 41, 184
Galle, P.R. 77
Ganchiku, Y. 98, 129
Gandhi, M. 96
Gao, Y. 133
Ge, N. 127
Ghassan, A.-A. 58
Gilliam, Y.M. 96
Girvan, A.C. 138
Goh, B.K.P. 84, 96
Goh, H.G. 176
Goh, S. 169
Gong, W. 102
Gong, Y. 133
Goto, R. 98, 100, 129
Gotoda, H. 158
Gracian, A.C. 106
Greten, T. 3
Guevarra, G.M.I. 197
Gwak, G.-Y. 82, 176
- Ha, J.S.K. 110
Hack, S. 107
Hagiwara, M. 159
Hakozaki, K. 49
Hakozaki, T. 49, 97, 185
Ham, C.B. 147
Hamaguchi, Y. 100
Han, B. 158
Han, B.H. 157, 193
Han, C. 133
Han, H.-S. 96, 184
- Han, J.-H. 145
Han, K.H. 81
Han, K.-H. 13, 104, 105, 107, 131, 132, 164, 191, 194
Han, M.-H. 145
Han, N.I. 182
Hao, N. 88
Harada, N. 103, 160
Hasegawa, K. 7, 14, 69, 83, 92, 96, 113, 160
Hashimoto, K. 66
Hatano, E. 50
Hayashi, H. 186
Hayato, S. 104
He, A.R. 107
Heo, J. 171
Heo, N.-Y. 191
Hernandez, M. 3
Hess, L.M. 138
Hiasa, Y. 147
Hirai, T. 49, 97, 185
Hiraoka, A. 147
Hirooka, M. 147
Hiroyoshi, J. 160
Hiroyuki, F. 64
Hiroyuki, T. 64
Hlaing, N.K.T. 140, 141, 161
Ho, C.H.M. 110
Ho, L.V. 159
Ho, M.-C. 90
Ho, S. 178
Honda, M. 104
Honda, S. 180
Hong, J. 163
Hong, T.H. 182
Hong, Y.J. 181
Hong, Y.M. 171
Hou, M.-C. 163
Hsiang, C.-H. 196
Hsiang, C.-W. 196
Hsu, C. 40, 110
Hsu, C.-H. 55, 107, 110, 127
Hsu, C.-S. 162
Hsu, H.-H. 124
Hsu, Y. 127
Hsueh, K.-C. 180
Hu, K. 129
Hu, K.-S. 114
Hu, T.-H. 96
hua, S. 124
Huang, A. 167
Huang, C.-C. 166
Huang, C.-T. 166
Huang, D.Q. 143
Huang, G.-S. 124
Huang, J. 27
Huang, K. 45
Huang, Q.D. 94
Huang, W.-Y. 85, 165, 196
- Huang, Y.-H. 13, 134, 163
Hung, E. 178
Hung, Y.-P. 134, 168
Hur, W. 111
Hwang, S.G. 191
- Ichida, A. 7, 83, 160
Igarashi, K. 104
Iizumi, T. 72
Ikeda, K. 90, 104, 105, 107
Ikeda, M. 13, 80, 107
Imai, K. 159, 186
Imamura, J. 98
Inagaki, Y. 113
Ishihara, A. 101
Ishikawa, H. 72
Ishiko, T. 186
Ishizawa, T. 7, 14, 83, 92, 113, 160
Iso, Y. 103, 160
Ito, K. 6
Ito, T. 101
Itoh, Y. 106
Itoi, T. 92
Itoyama, R. 186
Iwasaki, T. 113
Izumi, N. 5, 123
- Jang, H. 135
Jang, J.W. 137, 152, 182, 194
Jang, J.Y. 108, 153, 161
Jang, S.-H. 145
Jang, S.Y. 191
Jang, W.I.L. 167
Jeng, K.-S. 166
Jeon, M.Y. 164
Jeon, W.K. 147
Jeong, B.-K. 91
Jeong, D. 144
Jeong, J.H. 157, 193
Jeong, S.W. 108, 153, 161
Jeong, Y.Y. 182
Jeyaraj, P.R. 84
Ji, J.-S. 126
Jiang, Z. 189
Jin, B. 189
Jin, S.Y. 153
Jin, Y.-J. 146
Jo, S. 167
Joh, J. 101
Jun, B.G. 108
Jun, C.H. 142, 148
Jung, J. 163, 195
Jung, J.H. 198
Jung, M.W. 148
Jung, S.O. 153, 154, 157
Jung, Y.J. 144
Jung, Y.K. 176
- Kaido, T. 100

- Kam, J.-H. 84
Kamachi, H. 89, 94, 99, 100, 155, 186
Kamiyama, T. 89, 94, 98, 99, 100, 129, 155, 186
Kamo, N. 100
Kaneko, H. 9
Kaneko, J. 7, 14, 83, 92, 113, 160
Kang, B.-Y. 111
Kang, H.-C. 91
Kang, J.H. 172
Kang, J.K. 167
Kang, K.J. 139
Kang, M.K. 191
Kang, S. 82, 153
Kang, S.H. 141
Kang, W. 82, 176
Kang, Y.-K. 127
Kanto, T. 89
Kao, J.-H. 28
Kao, J.-T. 150
Kasai, Y. 92
Katagiri, S. 65
Kato, T. 113
Kawakami, Y. 54
Kawamura, N. 98, 100, 129
Kawamura, Y. 47
Kay, C.-S. 85
Ke, S. 133
Kholili, U. 125
Khuntikeo, N. 36
Kikuko, I.H. 192
Kim, B.I. 147
Kim, B.K. 131, 132, 164, 191
Kim, C.W. 152, 182
Kim, D.G. 182
Kim, D.S. 164
Kim, D.Y. 131, 132, 162, 164, 191, 194
Kim, E.J. 167
Kim, E.S. 167
Kim, G.-A. 143
Kim, G.R. 109
Kim, H.I. 178
Kim, H.J. 147, 194
Kim, H.S. 87
Kim, H.S. 108, 142
kim, H.S. 153
Kim, H.S. 161
Kim, H.Y. 152, 182
Kim, J. 82, 101, 176
Kim, J.H. 91, 144
Kim, J.-H. 145
Kim, J.H. 163, 176, 182, 195
Kim, J.-W. 144
Kim, J.-Y. 82
Kim, K. 139
Kim, K.-H. 68
Kim, K.M. 155, 189, 195
Kim, K.S. 162
Kim, K.W. 156, 172
Kim, M.A. 135
Kim, M.-J. 91, 96
Kim, M.-S. 167
Kim, M.Y. 141
Kim, N. 85
Kim, N.H. 147
Kim, S. 142, 155, 171
Kim, S.G. 108, 153, 161, 198
Kim, S.H. 152, 153, 154, 157, 194
Kim, S.J. 157
Kim, S.M. 111, 148
Kim, S.S. 139
Kim, S.U. 131, 132, 164, 176, 191
Kim, S.W. 135
Kim, S.Y. 87, 163, 172, 195
Kim, T.H. 91, 176
Kim, T.-S. 139
Kim, T.-Y. 135
Kim, W. 144, 167
Kim, W.J. 111
Kim, Y.A. 131, 132
Kim, Y.D. 108
Kim, Y.H. 96, 139
Kim, Y.J. 135, 170
Kim, Y.K. 172
Kim, Y.-K. 180
Kim, Y.S. 108, 153, 161, 198
Kim, Y.-Y. 91
Kimura, K. 101
Kimura, T. 85
Kishi, Y. 113
Kitano, S. 56
Kleiner, D. 3
Knox, J. 184
Kobayashi, A. 100
Kobayashi, M. 104
Kodama, T. 31
Koh, K.C. 82, 176
Koh, Y.X. 84
Koizumi, T. 49, 97, 185
Koji, I. 64
Kojima, T. 109
Kokudo, N. 1, 6, 69, 113, 184
Kokudo, T. 14, 92, 113
Kondo, T. 180
Kong, D. 189
Koshizuka, Y. 100
Kouji, N. 97
Kow, A.W.C. 143
Kow, W.C.A. 94
Kubo, S. 101
Kubota, K. 103, 160
Kudo, M. 11, 13, 48, 76, 81, 90, 104, 105, 106, 107, 123, 127, 183
Kumada, H. 104
Kuromatsu, R. 106
Kurosaki, M. 80
Kusano, T. 49, 97, 185
Kwee, S. 164
Kwee, S.A. 97, 173
Kwok, G. 15
Kwon, C.D. 101
Kwon, H.J. 145
Kwon, J.H. 152, 178, 182, 183
Kwon, S.Y. 144
Kwon, Y. 184
Kyaw, A.M.M. 161
Lai, H.-C. 150
Lai, M.-W. 114
Le, H.T. 159
Le, L.V. 159
Le, T. 35
Le, T.V. 159
Lee, B. 184
Lee, B.K. 146
Lee, B.S. 153, 154, 157
Lee, C.-H. 135
Lee, D. 155, 189, 195
Lee, D.H. 146
Lee, F.A.S. 110
Lee, H.A. 132, 164, 176
Lee, H.C. 155, 163, 178, 189, 195
Lee, H.L. 182
Lee, H.R. 152
Lee, H.W. 162, 171
Lee, I.-C. 163
Lee, I.J. 109
Lee, J. 44, 60, 169
Lee, J.H. 82, 176
Lee, J.-H. 135, 170
Lee, J.I. 171
Lee, J.J.X. 136
Lee, J.M. 198
Lee, J.S. 131, 132, 164, 191
Lee, J.-W. 146
Lee, J.W. 193
Lee, J.Y. 183
Lee, K.-H. 107, 135
Lee, K.S. 171
Lee, M.H. 198
Lee, M.S. 107
Lee, R.-C. 134, 163
Lee, S. 96, 156
Lee, S.H. 108, 153, 161
Lee, S.-J. 145
Lee, S.M. 180
Lee, S.S. 172
Lee, S.U. 157, 193
Lee, S.W. 152, 182
Lee, S.Y. 84, 169
Lee, T.Y. 182, 187
Lee, V.H.F. 85
Lee, V.W.Y. 110
Lee, Y.B. 135
Lee, Y.-H. 90
Lee, Y.K. 146
Lee, Y.-S. 155, 176

- Lee, Y.S. 189
Lei, H.-J. 134
Lencioni, R. 105, 183, 184
Leow, W.Q. 169
Leung, R.C.Y. 15
Li, B. 15
Li, G. 151
Li, H. 169
Li, J. 96
Li, L. 96
Li, M. 129
Li, X.-L. 187
Li, Z. 158
Liang, P.-C. 90, 110
Lii, A.-L. 2
Lim, C.J. 148
Lim, H.-Y. 127
Lim, J. 169
Lim, S. 169
Lim, S.H. 198
Lim, T. 169
Lim, Y.-S. 143, 155, 163, 189, 195
Lin, C.-C. 166
Lin, C.-K. 166
Lin, C.-L. 114
Lin, C.-S. 196
Lin, H.-H. 124
Lin, H.-M. 13
Lin, S. 140, 141
Lin, Z.-Z. 110
Liu, B. 107
Liu, C.-A. 134
Liu, C.-H. 124
Liu, X. 184
Liu, Y. 102
Liu, Y.-W. 150
Lo, C.-H. 165
Loh, J. 169
Loh, T. 169
Loilome, W. 36
Lopez, C. 105
Lopez, C.L. 123
Lu, S. 129
- Ma, H. 125
Ma, J. 88
Ma, K.W. 15
Ma, L. 3
Ma, Y.T. 107
Maimunah, U. 125, 192
Maimunah, U.M. 193
Maki, H. 83
Makita, C. 109
Makuuchi, M. 65
Malabanan, M.M.H. 197
Malavasi, F. 169
Mann, H. 183, 184
Martin, S. 3
Masahiro, H. 64
- Matilla, A. 106
Matsuda, K. 49, 185
Matsumoto, T. 160
Matsumura, M. 98
Matsuno, N. 159
Matsuo, M. 109
Maung, M.Z. 140, 141
Maung, S.T. 34
Melero, I. 106
Meng, Z. 105
Michitaka, K. 147
Midorikawa, Y. 26, 99
Mihara, F. 6
Mihara, Y. 21
Minami, Y. 48
Mishima, K. 104
Misir, S. 123
Miyata, T. 186
Miyata, Y. 113
Miyayama, S. 10, 13
Miyazaki, T. 101
Mizumoto, M. 72
Mody, K. 107
Mok, J.S.R. 143
Mok, S.R.J. 94
Moon, H.H. 157
Moon, J.S. 146
Moon, M.J. 182
Morgan, S. 183, 184
Mori, S. 103, 160
Moris, D. 84
Mufida, A.Z. 125, 192
Murakami, M. 49, 97, 185
Murofushi, K. 72
Muto, J. 98
Myint, K.T. 140, 141
- Na, G.-H. 145
Na, G.H. 182
Na, M.J. 87
Na, S.K. 180
Nagatsu, A. 89, 94, 99, 155, 186
Nakagawa, H. 32
Nakagawa, S. 186
Nakai, K. 72
Nakajima, K. 104
Nakano, M. 65
Nakano, S. 158
Nakano, T. 133
Nakao, Y. 186
Nakazawa, A. 83
Nam, H.C. 152
Nam, J.M. 109
Nam, S.W. 87, 178, 182, 183
Naoto, M. 64
Neely, J. 106
Nemoto, S. 98
Newell, E. 169
Ng, H. 169
- Ng, I.O.-L. 22
Ng, K. 136
Nguyen, D.S.H. 35
Nguyen, Q.N. 35
Ni, C.-F. 126
Nie, D. 15
Ninomiya, T. 147
Nishioka, T. 101
Niu, H. 116
Nogaki, K. 49, 185
Nojiri, K. 83
Nouso, K. 46, 152
Nufika, R. 138
Numajiri, H. 72
Numata, K. 106, 107
Nusi, I.A. 125, 192
- Ogasawara, S. 17
Ogawa, C. 11
Ogawa, K. 129
Oh, K.S. 193
Ohbora, A. 109
Ohdan, H. 69
Ohira, G. 101
Ohnishi, K. 72
Ohno, T. 73, 133
Okabe, H. 186
Okada, H. 152, 180
Okamaoto, M. 133
Okubo, H. 74
Okumura, K. 180
Okumura, T. 72
Okusaka, T. 104, 127
Ome, Y. 98
Ong, C. 169
Onishi, H. 152
Ono, K. 109
Ooi, L.P.J. 84
Orimo, T. 89, 94, 99, 155, 186
Othiwi, Y.L. 138
Otsuka, Y. 9
Oyama, A. 152
Ozaki, T. 104
- Paik, E.K. 167
Paik, S.W. 82, 176, 191
Paik, Y.-H. 82, 176
Palaniappan, M. 96
Palmer, D. 105
Pan, J. 97
Park, C.H. 142
Park, E.T. 193
Park, H.H. 163
Park, H.J. 157, 167, 172
Park, I.-Y. 145
Park, J.G. 193
Park, J.H. 167
Park, J.-W. 39, 105, 184
Park, J.Y. 131, 132, 164, 191

- Park, K.H. 103, 160
Park, K.R. 109
Park, M.J. 139
Park, N.R. 137
Park, S.H. 172
Park, S.Y. 142
Park, T.Y. 146
Park, Y.H. 167
Park, Y.J. 171
Park, Y.N. 20
Peng, C.Y. 96
Peng, C.-Y. 150
Pham, C.P. 35
Piscaglia, F. 104, 105, 107
Pitoyo, F.L. 125, 193
Pracht, M. 105
Purbayu, H. 125, 192
pyo, K. 181
- Qin, S. 104, 105, 107, 112, 123, 183
Qin, S.-K. 96
Qiu, H. 133
Quek, P. 84
- Rao, W. 158
Rau, K.-M. 107
Reig, M. 106
Ren, M. 104, 123
Ren, Z. 104, 107, 120, 125, 127, 129, 177, 183, 192
Ren, Z.-G. 114
Rho, S.Y. 162
Rim, C.H. 91
Rou, W.S. 153, 154, 157
Ryoo, B.-Y. 107, 112, 123, 181
Ryu, J.S. 142
Ryu, S.H. 146
Ryu, T. 161
- Sabai, K. 169
Saito, A. 65
Saito, K. 90, 105, 107
Saitou, Y. 159
Sakamoto, M. 19
Sakamoto, N. 131
Sakamoto, Y. 89, 94
Sakata, M. 152
Sakurai, H. 72
Sakuraoka, Y. 103, 160
Sangro, B. 106, 183
Santoro, A. 106
Sarashina, K. 158
Sato, M.M. 173
Scheele, J. 112
Sekino, Y. 72
Sempokuya, T. 97
Seo, A.N. 145
Seo, C.W. 139
Seo, K.I. 157
- Seo, K.I.L. 193
Seo, Y.S. 132, 164, 176
Seong, J. 70, 85, 91, 194
Setiawan, P.B. 125, 192, 193
Seyama, Y. 98
Shao, Y.-Y. 110
She, W.H. 15
Shen, P.-C. 196
Shen, Y. 106
Shi, B. 189
Shi, W. 133
Shi, Y.-H. 114
Shiba, S. 133
Shibuya, K. 73, 133
Shigesawa, T. 131
Shih, T.T.-F. 110
Shih, Y.-L. 124
Shiina, S. 8
Shim, D.J. 183
Shim, J.H. 155, 178, 189, 195
Shimada, K. 96
Shimada, S. 89, 94, 99, 155, 186
Shimamura, T. 69, 98, 100, 129
Shimizu, S. 72
Shimizu, T. 103, 160
Shin, D.H. 157
Shin, Y. 101
Shin, Y.R. 178
Shinkawa, H. 101
Shirabe, K. 133
Shiraha, H. 152
Shirai, H. 100
Shiraki, T. 103, 160
Shirata, C. 92, 113
Sim, X.N. 169
Sinn, D.-H. 82
Sinn, D.H. 176
Sithithaworn, P. 36
Sofue, K. 63
Sohn, W. 147
Song, B.-C. 180
Song, D.S. 152, 182
Song, G.-W. 156
Song, J.-J. 126
Song, M.J. 152
Spahn, J. 107
Stein, S. 107
Strasser, S. 96
Su, C.-W. 163
Su, S.-C. 180
Suda, G. 131
Suga, Y. 147
Sugihara, T. 138
Sugihartono, T. 125, 192
Sugii, S. 158
Sugimoto, K. 92
Sugino, H. 180
Suh, K.-S. 67
Suh, S.J. 176
- Suh, Y.J. 146
Suk, K.-S. 12
Sulistiawati, E. 138
Sumi, Y. 159
Sun, H.-C. 187
Sun, Z. 86
Sung, M. 104, 107
Sung, P.S. 152, 182, 194
Surendran, S.P. 182
Suzuki, T. 103
- Tago, K. 103, 160
Tai, D. 169
Tai, D.W.M. 136
Tak, K.Y. 152
Tak, W.Y. 123
Takahashi, H. 106, 159
Takaki, A. 152
Takakuwa, E. 180
Takamoto, T. 75
Takayama, T. 26, 99
Takehara, T. 31
Takemura, N. 6, 96
Takemura, S. 101
Taketomi, A. 4, 89, 94, 98, 99, 100, 129, 155, 180, 186
Takeuchi, H. 92
Tamai, T. 90, 104, 105, 107
Tan, P.S. 94, 96, 143
Tanaka, A. 149
Tanaka, O. 109
Tanaka, S. 101
Tang, B. 114, 125, 129, 177
Tang, C.N. 51
Tang, V. 15
Taniguchi, T. 109
Tanimoto, M. 92
Tanizawa, Y. 138
Tateishi, R. 25, 107
Tauchi, J. 101
Taura, K. 100
Tay, B.W.R. 143
Tay, W.R.B. 94
Teh, C. 37
Teo, J.-Y. 84
Tey, Y.Q. 94, 143
Thinkhamrop, B. 36
Tian, M.-X. 114
Tiirikainen, M.I. 173
Titapun, A. 36
Toh, H.C. 169
Tomioka, K. 97
Tran, C.D.L. 35
Tsang, S. 15
Tse, E. 96
Tseng, K.-C. 162
Tsolmon, J. 33
Tsubouchi, E. 147
Tsunenari, T. 113

- Tun, K.T. 140, 141
Tun, K.Z. 161
Tun, T. 140
- Ueda, K. 61
Uemoto, S. 69, 100
Ueshima, K. 90, 105
Um, S.H. 164, 176
- Verret, W. 107
Vlahovic, G. 183, 184
Vogel, A. 105, 123, 127
Vu, Q.V. 159
- Wada, N. 152
Wada, Y. 49, 97, 185
Wakabayashi, G. 53, 104
Wang, C.-C. 150
Wang, C.-K. 13
Wang, H.-J. 96
Wang, J. 133
Wang, N. 80
Wang, X. 52, 102
Wang, X.W. 3
Wang, Y. 120, 127, 192
Wang, Z. 158
Watanabe, A. 133
Watanabe, M. 98, 100, 129
Weng, M.-T. 166
Wien, E.A. 97
Win, K.M. 34
Win, N.K.T. 141
Win, S.T.S. 34
Winoto, I. 138
Won, K.S. 139
Wong, F.C.S. 110
Wong, L. 136, 164
Wong, L.L. 97, 173
Wong, N.S.M. 110
Woo, H.Y. 171
Woo, S.H. 141
Wu, C.-C. 162
Wu, C.-H. 59, 90
Wu, L. 158
Wu, L.-W. 126
Wu, M.-S. 126
- Wu, W. 102
Wu, X. 102
Wyrwicz, L. 104
- Xiang, Z.-L. 88
Xu, X. 192
- Yagi, S. 100
Yamamoto, J. 113
Yamamoto, M. 65
Yamashita, Y. 186
Yamazaki, T. 97, 185
Yamazoe, S. 101
Yang, G. 87
Yang, H.D. 87
Yang, J.-F. 196
Yang, J.H. 189
Yang, J.-M. 96
Yang, J.M. 152, 182
Yang, K.M. 167
Yang, S. 82
Yang, S.-F. 180
Yang, X.-R. 167
Yano, H. 21
Yao, R. 120
Yao, S. 100
Yasunaka, T. 152
Yau, T. 15
Yeh, C.-T. 114
Yen, C.-J. 127
Yeon, J.E. 176
Yeong, J. 169
Yeung, C.S.Y. 110
Yim, H.J. 176
Yim, S.Y. 176
Yin, X. 114, 125, 129
Yip, S. 178
Yip, W.W.Y. 110
Yokoo, H. 64, 159
Yokoyama, R. 158
Yoo, B.C. 144
Yoo, C. 79, 181
Yoo, H.J. 167
Yoo, J.-J. 108, 153, 161
Yoo, K. 191
Yoo, S. 183
- Yoo, S.H. 152, 178, 182
Yoon, G. 145
Yoon, J.H. 148
Yoon, J.-H. 30, 104, 135, 139, 170
Yoon, K.H. 182
Yoon, K.T. 171
Yoon, S.K. 111, 137, 152, 182, 194
Yoon, S.M. 163, 195
Yoshimasu, Y. 92
Yoshio, S. 89
You, Y.K. 182, 187
Yu, C.-Y. 124
Yu, J.H. 146
Yu, S.J. 135, 170
Yuan, B. 88
Yuan, B.-Y. 88
Yuan, J. 114, 129
Yuen, B. 178
Yun, B.C. 157, 193
Yusa, T. 186
Yusuf, I. 138
- Zang, Y. 158
Zani Jr., S. 84
Zeng, Z. 88, 132, 135
Zeng, Z.-C. 85, 87, 88, 116
Zhang, F. 114, 129
Zhang, H. 130, 189
Zhang, L. 88, 116, 120, 125, 126, 127, 192
Zhang, N. 86
Zhang, Z. 29, 100
Zhao, Q. 132, 135
Zhao, X.-M. 87
Zhao, Y. 3
Zhong, B.-Y. 126
Zhou, D. 112
Zhou, J. 18, 167, 184
Zhu, A. 127
Zhu, X. 96
Zhu, X.-D. 187
Zhu, X.-L. 126
Zhu, Y. 86
Zhuang, Y. 87, 88