Hepatocellular Carcinoma

Eastern and Western Experiences

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Guest Editors

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Abstracts

Oral Presentations

O-1

A Worldwide Survey of the Current Practice of Liver Surgery

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Background: Liver resection remains the mainstay of curative treatment for liver malignancies. A variety of preoperative assessments and surgical techniques have improved the short-term and long-term outcomes of liver resection in patients with liver tumors. In the same time, laparoscopic hepatectomies have been increasingly performed. The object of the present study is to survey the current practice of liver surgery in high volume centers in the world.

Methods: A questionnaire on preoperative assessment for liver surgery, open hepatectomy, and laparoscopic hepatectomy was sent to 94 liver centers in the world.

Results: Forty-two centers (45%) responded to this survey (29 Asian, 9 European, and 4 North American countries). All but one of the centers evaluated the future liver remnant (FLR) volume, and 95% of them performed preoperative portal vein embolization (PVE) to increase the FLR volume. In half of the centers, the required FLR was over 30% in patients with normal liver, and 45% in patients with cirrhotic liver. To reduce the intraoperative blood loss, half of the centers routinely used Pringle's maneuver, and 85% restricted the intraoperative fluid infusion to reduce the central venous pressure. More than 10 laparoscopic hepatectomies were performed in 62% of the centers, and more than 30 were performed in 26%, respectively. Laparoscopic major hepatectomies were performed in 24%. Two thirds answered that laparoscopic approach is feasible in donor hepatectomy.

Conclusion: Evaluation of resectional hepatic volume in patients with normal or cirrhotic liver and usage of preoperative PVE become essential manner in half of the centers. Reduced blood loss has been achieved using Pringle's maneuver, restriction of fluid infusion, and a variety of surgical devices. Laparoscopic approach has been increasingly used in the world.

O-2

Surgical Strategy for HCC Using ICG Test

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Hepatocellular carcinoma (HCC) usually develops in patients with underlying chronic liver diseases caused by hepatitis virus infection, alcohol consumption, steatohepatitis and so on. Inappropriate volume removal of functioning liver induces liver failure in patients with chronic liver disease. To prevent postoperative hepatic failure, several criteria for safe hepatic resection have been reported. Makuuchi's criteria for hepatectomy is simple to apply and known widely. It consists mainly of two factors; serum total bilirubin level and ICG 15 value. In patients who have preoperatively elevated serum total bilirubin level between 1.0 mg/dl and 2.0 mg/dl, tumor enucleation or limited liver resection is acceptable. In patients with serum total bilirubin level less than 1.0 mg/dl, liver volume to be resected is determined based on ICG 15 value. In case of ICG 15 value less than 10%, up to 2/3 of total liver volume could be removed, up to 1/3 of total liver volume could be removed in case of ICG 15 value between 10 to 19%, subsegmentectomy could be indicated in case of ICG 15 value between 20 to 29%, limited resection should be chosen in case of ICG 15 value between 30 to 39%, and in case of ICG 15 value more than 40% just enucleation is appropriate.

Since 1990, we have performed hepatectomy for HCC patients according to the Makuuchi's criteria. This time we analyzed 802 HCC patient's records retrospectively.

As for hyperbilirubinemia after hepatectomy, 141 patients (17.6%) had over 1.0 mg/dl serum total bilirubin elevation after hepatectomy compared to that of preoperative one. Among them, 30 patients (3.7%) had elevated serum total bilirubin level more than 2.0 mg/dl after hepatectomy including 4 patients with over 5 mg/dl serum total bilirubin elevation postoperatively. Hospital mortality was 0.37%; 3 patients death due to hepatic failure.

The low rate of postoperative hepatic failure indicates that the Makuuchi's criteria for hepatectomy is simple and reliable. I will talk about the detail results of 802 patients and refer to factors influencing serum total bilirubin elevation after hepatectomy.

O-3

Can Sinusoidal Injury and Splenomegaly be Predicted by AST/Platelet Ratio Before Performing Chemotherapy in Patients with Colorectal Cancer Liver Metastases?

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Background/Aim: Whether or not to perform neoadjuvant chemotherapy (NAC) is now being debated in patients with initially 'resectable' colorectal cancer liver metastases (CRCLM). One of the disadvantages of NAC is oxaliplatin-induced sinusoidal injury (OSI) which cannot be disregarded due to high grade morbidity after major hepatectomy (Nakano H, et al. Ann Surg 2008). Although bevacizumab (BV) reduces the incidence of OSI, detecting oxaliplatin-naïve patients is still important before performing oxaliplatin-based NAC. To find out oxaliplatin-naïve patients before performing chemotherapy, AST/platelet ratio (APR) before chemotherapy was analyzed as a predictor of oxaliplatin-induced sinusoidal injury and splenomegaly (OSIS).

Patients and Methods: The risk of OSIS concerning major morbidity after a right hemihepatectomy was investigated, and then whether the APR before chemotherapy can predict OSIS was also investigated in the other patients with CRCLM. Splenic volume was measured with CT volumetry before and after chemotherapy, and the APR was also measured.

Results: Major complication more significantly occurred in OSIS group than in non-OSIS group (56% vs. 15%, $p < 0.05$) among 77 patients undergoing right hepatectomy. Among 103 patients with CRCLM, APR before chemotherapy (> 0.15) was significantly associated with splenomegaly ($> 30\%$) during 12 weeks of oxaliplatin-based chemotherapies ($p < 0.05$). The incidence of adverse events during 12 weeks of oxaliplatin-based chemotherapies was significantly higher in patients with APR > 0.15 before chemotherapy than in those with APR < 0.15 . ($p < 0.05$). FOLFOX and XELOX/BV regimens were significantly associated with splenic volume increase compared to FOLFOX/BV ($p < 0.01$).

Conclusion: OSIS was significantly associated with major morbidity after right hepatectomy. The FOLFOX and XELOX/BV induced OSIS, especially splenomegaly after oxaliplatin-based chemotherapy but FOLFOX/BV did not. OSIS may be predicted if the APR before chemotherapy was 0.15 or more. Whether or not to perform NAC can be considered if APR was 0.15 or more in patients with initially resectable CRCLM.

O-4

Where is the Limit of Extensive Hepatectomy Considering the Hepatic Volume and Function?

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With the increasing frequency of complex and extensive procedures, the assessment of FLR (Future Liver Remnant) volume has become critical in minimizing postoperative hepatic insufficiency and liver-failure related death and in determining the effectiveness of PVE (portal vein embolization). The trophic effects of PVE are specifically beneficial in patients with anticipated marginal FLR volumes, those with liver injury due to modern systemic therapies and those with chronic liver disease.

We previously described the minimal necessary FLR volume as $>20\%$ for patients with normal livers, $>30\%$ for patients with extensive preoperative chemotherapy or with histopathologic injuries (fibrosis and chemotherapy associated liver injury), and $>40\%$ for patients with cirrhosis. We also previously reported high sensitivity and specificity in predicting hepatic dysfunction and complications when the FLR was combined with a degree of hypertrophy (DH) of $>5\%$. DH is the difference between the FLR after PVE and the FLR before PVE. Although these cutoffs are a useful guide to predict surgical outcomes, they do not give any information regarding liver function.

In a more recent study, we analyzed a novel dynamic measure for post-PVE FLR volume, the kinetic growth rate (KGR) defined as the DH divided by the number of weeks between the pre and post PVE FLR measurements. As such, KGR defines a functional response to PVE based on speed of regeneration. The analysis focused on patients with colorectal liver metastases and indicated that KGR predicts postoperative hepatic insufficiency (defined as a postoperative peak bilirubin >7 mg %) more effectively than the conventional measures of FLR and DH. In this population, a KGR of at least 2.0% per week protects from hepatic complications and liver failure related death. In patients without cirrhotic liver disease, hepatic insufficiency is a strong predictor of death from liver failure. The study of KGR confirms previous studies indicating that liver-failure related death eventually develops in approximately one third of patients with postoperative hepatic insufficiency.

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O-5

Hepatic Transection Using LigaSure

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The clamp-crush (CC) technique is considered the current standard technique for liver transection. There are two steps in conventional liver transection using the CC technique; the first is to expose the vessels including the hepatic vein and Glisson's sheath, and the second is to ligate or ablate the residual tissues by electric cautery. LigaSure tissue fusion, like LigaSure vessel sealing, uses the body's own collagen and elastin to create a permanent fusion zone. In a randomized clinical trial, use of the LigaSure system reduced operation time and blood loss in patients undergoing various surgical procedures including gynecological, colorectal, urological, and general surgery. When used in liver transection, LigaSure can seal and cut vessels faster than manual ligation and is more consistent and reliable than conventional electric cautery. We previously reported that use of a prototype LigaSure system plus CC technique during liver transection allows rapid and safe division of liver parenchyma. In the randomized clinical trial, 60 patients (n = 30 in each group) with liver pathology were randomized to undergo liver resection with either the LigaSure system or with conventional clamping methods. Patients were stratified according to tumor size (<5 or >5 cm), type of hepatectomy (minor or major), and liver damage (normal or injured). Estimated blood loss during liver transection was used as the primary end point, whereas liver transection speed and morbidity rate were used as secondary end points. There were no hospital deaths. The median blood loss during liver transection was less in the LigaSure than in the conventional group (200 vs 322 mL; $P = .185$). The amount of blood loss during minor hepatectomy was significantly less in the LigaSure than in the conventional group (186 vs 412 mL, $P = .012$). The liver transection speed was significantly faster in the LigaSure than in

the conventional group (2.3 vs 1.6 cm²/min, $P < .001$). The number of ties required during liver transection was significantly less in the LigaSure than in the conventional group (6 vs 69 ties, $P < .001$). The morbidity rate was similar when comparing the 2 groups, indicating that the LigaSure sealing device and conventional methods had comparable efficacy in sealing the bile duct in the portal triad. Postoperative bile leak was observed in 1 patient (3%) in the LigaSure group and in 3 patients (9%) in the conventional group ($P = .301$). We showed that the LigaSure system is an effective and safe tool for decreasing liver resection time. In this presentation, we will show you the video of the hepatic resection using LigaSure.

O-6

New Stage Two Hepatectomies: ALLPS

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Objectives: To give an overview over the development and current status of ALPPS (Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy) and compare it with conventional approaches for liver tumors that are not resectable in one stage.

Topics of the Presentation: Extensive liver tumors are traditionally removed using PVE or PVL to induce an increase of the future liver remnant volume, followed by resection after 4–8 weeks. ALLPS combines PVL and complete parenchymal transection during a first stage without removal of the diseased hemiliver, followed by early hepatectomy within 1–2 weeks. The current literature consists mostly of case series demonstrating rapid hypertrophy and a high perioperative morbidity and mortality. However both PVE and PVL are procedures with limited efficacy since only 69–83% of patients eventually proceed to the second stage of curative resection, mostly due to tumor progression. While some consider tumor progression in the waiting interval as a useful selection mechanism to avoid an extensive second stage resection in patients with unfavorable tumor biology, others have hypothesized that the long-time interval, rather than tumor biology between the two stages, is responsible for the high degree of disease progression between stages. Recently a multicenter retrospective analysis was performed to evaluate whether ALPPS is better at achieving complete resection (R0) at the early but highly significant endpoint 3 months. In this study patients undergoing ALPPS in four international centers were compared with patients who underwent conventional two-stage procedures. 77% of ALPPS patients achieved R0 resection at three months compared to 58% in the conventional arm (OR 2.74, $p = 0.031$). 90-day mortality in ALPPS and PVE/ PVL were 14.9% and 6.0% respectively ($p = 0.20$). The concerns about increased tumor progression in ALPPS group could not be confirmed in our study.

Conclusions: There is now evidence that ALPPS is better than conventional two-stage procedures to achieve complete resection. This increased resection rate however come at an possibly increased morbidity and mortality. These results support the need for longer follow-up and randomized controlled trials (RCT) to definitively delineate the role of ALPPS in liver surgery.

O-7

Anterior Approach During Hepatectomy

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The anterior-approach right hepatectomy was introduced by Kazuo Ozawa in 1992. It is particularly suitable for treating large right-liver tumors. With this technique, prolonged rotation of the right liver could be avoided, thereby precluding interruption of the inflow and outflow of the liver and preserving the liver function. In the technique, after division of the right portal vein and the hepatic artery, the liver is transected by CUSA from the anterior surface of the liver down to the liver hilum and caudate lobe, thereby exposing the inferior vena cava. Short hepatic veins and right hepatic vein are then dissected from the front and individually ligated. After dividing the triangular ligament, the right liver could be removed.

In a prospective randomized trial on patients with hepatocellular carcinoma, we demonstrated that the anterior-approach right hepatectomy resulted in less major bleeding, less dissemination of cancer cells into the systemic circulation and longer overall survival when compared with the conventional technique.

The anterior approach is also applicable to left hepatectomy. Moreover, it is a favorable approach when the bile duct in the right liver is infected and obstructed or when abscess is present in the right liver, as without forceful rotation of the right liver, infected material would not be squeezed into the systemic circulation.

O-8

Isolated Segment 1 Resection

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Background: I have developed a procedure of isolated segment 1 resection ('high dorsal resection') of the liver to resect a hepatocellular carcinoma (HCC).

Methods: The segment 1 was classified into Spiegel's portion (left-sided area), process portion (right-sided lower

area), and caval portion (right-sided pericaval area). In patients with good liver function, the segment 1 with HCC was removed en-bloc with right or left lobe, or with neighbor segment. To the patients with cirrhosis, this specific procedure was applied. In the operation, liver transection advances on the plane that starts from the right border of segment 1, through beneath the right and middle hepatic veins, and focuses to Arantius' ligament (transection attempts to reach as 'high' as the root of the hepatic veins only by 'dorsally' approach).

Results: We performed liver resection in 895 patients with HCC, of whom 107 had had HCC in the segment 1. In 52 patients with an HCC at Spiegel's portion or process portion, the HCC was removed by local resection of segment 1 ($n = 34$), or by combined resection with lobe or other segment ($n = 18$). In 55 patients with an HCC at caval portion, the segment 1 were resected with extended lobectomy ($n = 11$) or segmentectomy ($n = 29$), and by high dorsal resection ($n = 15$). The median blood loss and operation time were 511cc (25–4,530) and 449 min (130–903), respectively. The operative morbidity rate was 22% and the mortality rate was 0%. Overall and recurrence-free survival rates at 5 years were 58% and 33%, respectively.

Conclusions: High dorsal resection is a reasonable procedure of choice for patients with HCC at caval portion of the segment 1.

O-9

A Novel Treatment Algorithm for Hepatocellular Carcinoma: Experience from a Single Chinese Center

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Background: Posthepatectomy liver failure (PHLF) is a feared complication after hepatic resection and a major cause of perioperative mortality. Although many criteria have been established for safe hepatic resection, there is currently no universal algorithm for treatment of hepatocellular carcinoma (HCC). We have establish a novel treatment algorithm for safe hepatectomy based on four variables: normal or cirrhotic liver, Child-Turcotte-Pugh score, the indocyanine green retention rate at 15 minutes (ICGR-15), and the ratio of reserved functional liver volume (RFLV) to standard liver volume (SLV).

Methods: A total of 2,457 patients underwent hepatic resection between January 2004 and December 2010 in Chinese PLA General Hospital, and 634 patients with HCC were eligible for final analyses. PHLF has been identified by the association of prothrombin time <50% and serum bilirubin >50 micromol/L (the '50–50' criteria), which were assessed at day 5 postoperatively or later. Swiss-Clavien's

Fig. 1. (for Abstract O-9)

algorithm, Tokyo University-Makuuchi's algorithm and our novel algorithm were adopted to divide patients into two groups on whether met those decision trees in sequence, and PHLF rate were recorded.

Results: The overall mortality and PHLF rate were 4.1% and 3.0%. 19 patients occurred PHLF, of which 8 patients died. Patients met Swiss-Clavien, Tokyo university-Makuuchi and the novel algorithm were 581, 573 and 622, whose PHLF rate were 2.75%, 2.62% and 2.73%, respectively. Cases satisfied the novel algorithm were significantly more than Swiss-Clavien's algorithm and Tokyo university-Makuuchi's algorithm ($p < 0.001$), nevertheless the latter two shared no difference ($p = 0.147$). The PHLF rate has no significant difference with respect to three decision trees.

Conclusion: Our novel algorithm expands indications for hepatic resection for liver tumor, and not increases the PHLF rate comparing with Swiss-Clavien's and Tokyo university-Makuuchi's algorithm, respectively. It would be a safe and effective algorithm for hepatectomy in patients with HCC.

O-10

Recent Progress of Systemic Chemotherapy for HCC

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Until the advent of sorafenib, there was no effective treatment option for patients with HCC who had reach a stage beyond the accepted indication for surgery, ablation or chemoembolization. Conventional chemotherapy had never shown a benefit in terms of survival and in most instances, it was associated to severe adverse events. The better knowledge of the molecular mechanisms leading to cancer progression identified angiogenesis as a relevant target and provided the basis for the evaluation of sorafenib. It inhibits the serine-threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR- β). Its oral administration induces a delay in tumor progression and this translated into a significant improvement in survival. Its benefit in survival has been proven in Western and Eastern populations and currently, constitutes the single systemic agent for advanced HCC. As a consequence, sorafenib is recommended in all clinical practice guidelines (AASLD, EASL, APASL, ASCO, ESMO, WGO) as based in the top degree of scientific evidence.

The success of sorafenib has triggered a major research to evaluate new agents that could further improve the benefits of sorafenib, or combinations of sorafenib with other agents. Simultaneously with this activity in 1st line, agents have been evaluated in 2nd line after failure or intolerance to sorafenib. Unfortunately, all these attempts have afforded negative results. Sunitinib and Brivanib failed in direct comparison versus sorafenib, and the same was described when combining sorafenib with erlotinib. Brivanib also failed in 2nd line and results of ongoing trials with everolimus and ramucirumab are eagerly awaited.

Hopefully, current research in better characterization and stratification of the patients according to clinical and molecular profile, will refine how patients are selected for a specific treatment regime and allow an optimised use of the new agents to be developed and even of some that may have been initially discarded.

O-11

Laparoscopic Anatomical Resection for HCC

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Background: The introduction of laparoscopic liver resection has a great impact on liver surgery especially in the treatment of HCC. Anatomical liver resection appears to be superior to nonanatomical liver resection in operative and oncological results. The aim of the present study was to describe the procedure of laparoscopic anatomical liver resection and to review a single institution's experience of laparoscopic liver resection (LLR) including totally laparoscopic liver resection (TLLR) and laparoscopy-assisted liver resection (LALR) as a minimally invasive surgery for liver cancer.

Methods: Anatomical liver resection was performed by Glissonian approach either with TLLR or LALR. Between May 1997 and December 2012, 323 patients underwent LLR for hepatocellular carcinoma (HCC) (107 patients), liver metastases (136), cholangiocellular carcinoma (CCC) (13), carcinoid (1), benign liver lesions (22), and living donor (39) and others (5). Operations included 173 TLLR (117 wedge resections, 24 left lateral sectionectomies, 22 major anatomical hepatectomy, 7 segmentectomy, and 3 others), 150 LALR (4 trisectionectomy, 24 right hepatectomy, 26 left hepatectomy, 3 central bisectionectomy, 10 right anterior sectionectomy, 11 right posterior sectionectomy, 38 donor hepatectomy, and others). Thirty-two percent of TLLR, 91% of LALR, and 60% (193/323) in total, were anatomical liver resection.

Results: Median operating time was 148, 302 min, and blood loss, 57, 246 ml for TLLR, LALR, respectively. One TLLR was converted to a LALR. Only 13 patients (4.0%) experienced

postoperative complications, 7 patients (2.2%) showed bile leakage, and 6 patients (1.9%) developed wound infections. Overall 5-year survival for HCC was 65%.

Conclusions: Laparoscopic anatomical liver resection can be performed safely for liver cancer. Procedures vary from hybrid to pure technique and seem to offer at least short-term benefits in selected patients. The number of anatomical resections has increased as our experience increases.

O-12

Adopting Gayet's Techniques of Totally Laparoscopic Liver Surgery in the USA

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Introduction: Professor Brice Gayet of the Institut Mutualiste Montsouris in Paris France has developed totally laparoscopic techniques for all segments of the liver. As a pioneer in the field of Minimally Invasive Hepatic-Pancreatic and Biliary (HPB) Surgery he started a Minimally Invasive HPB Fellowship in 2006.

Methods: A retrospective review of all hepatic cases performed by a single surgeon since completing a minimally invasive HPB fellowship was undertaken.

Results: From Nov 2007 to October 2012 a total of 80 liver resections were done, of which 73 were begun with the intention of completing the case laparoscopically. Of these more than 90% were completed laparoscopically and 88% were for malignant disease.

Discussion: One of the foundation of Professor Gayet's techniques is the low lithotomy or 'French' position and the utilization of a small robotically-controlled laparoscope holder that is sterilizable and considerably more economic than complete surgical systems. Prototypes exist of robotically-controlled hand-held laparoscopic instruments that unlike the complete surgical system, enable surgeons to maintain a sense of touch (haptics).

Conclusions: Proper training in minimally invasive HPB techniques can be obtained with surgeons able to independently perform laparoscopic major hepatectomies without senior minimally invasive back-up. Furthermore, miniature and more affordable robotics may enable more surgeons to enjoy the benefits of minimally invasive surgery while maintaining patient safety and minimizing the rising burden of healthcare costs worldwide.

O-13

Role of Laparoscopic Hepatectomy in the Treatment of Hepatocellular Carcinoma in Taiwan

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Hepatocellular carcinoma (HCC) is the third most common malignancy in Taiwan. There were more than 10,000 new diagnosed cases and over 8,000 patients died of HCC in 2011. In the early stage of HCC, hepatectomy is a treatment of choice for patients with preserved liver function and performance status.

In Taiwan, the first laparoscopic hepatectomy for HCC was reported in the literature in 1988. However, the experience was only accumulated in very few medical centers. In the last three years, the number of the cases of laparoscopic hepatectomy increased rapidly. According to a national registration from the seven major medical centers in Taiwan, 83 out of 122 patients received laparoscopic hepatectomy (68%) were diagnosed with HCC in 2011, and most of the procedures were done purely laparoscopically. Minor resection (wedge resection (57%); lateral sectionectomy (19%)) was the most common procedure while major hepatectomy; including right (1.6%), left (4.9%), and central hepatectomies (4.9%), accounted for less than 12%. The conversion rate was 4.9%. One mortality was due to post-operative sepsis.

Laparoscopic hepatectomy could be considered as a routine procedure for patients in the early stage of HCC. The dissemination of the surgical skills and experience and the reimbursement of the expenses on medical devices by government insurance could encourage surgeons and patients to opt for this procedure so as to improve the post-operative outcome.

O-14

Laparoscopic Liver Resection for Hepatocellular Carcinoma: Korean Experiences

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The development of laparoscopic liver resection has been slow due to the technical difficulties. Therefore, laparoscopic liver resection has been limited to easily accessible lesions. Recently this procedure is well applied to hepatocellular carcinoma. However until now, the indications for laparoscopic liver resection have been tumors in the peripheral portion of the antero-lateral segments of the liver (segments II, III, V and VI and the inferior part of IV according to the classification of Couinaud). With growing interest in laparoscopic liver resection, there have been many attempts to apply this technique in difficult locations. The lesions in the posterior or superior part of the liver (segments I, VII, VIII and the superior part of IV), which are considered to be poor indications for laparoscopic liver resection have been reported to be successfully operated by laparoscopic surgery. Accordingly, this laparoscopic approach has become similar to open surgery in many ways. One of major advancements in laparoscopic liver resection is anatomic liver resection including major and minor resection. Laparoscopic mono and bisegmentectomy has been possible as well with accumulation of experiences. If we name whole monosegmentectomy and bisegmentectomy, there may be variety of anatomic liver resection. The common representative of bisegmentectomy is left lateral sectionectomy, right anterior sectionectomy right posterior sectionectomy. The common operative types of monosegmentectomy are S4, S5, S6 monosegmentectomy, etc. Central bisectionectomy will be also discussed. The Glissonian approach has been useful for these types of anatomic liver resection. The difficulty of controlling hemorrhage has been overcome by performing meticulous surgical techniques with the newly developed instruments and intraoperative sonography has been used to locate the lesion and guide the resection plane even for deep-seated or invisible lesions. Further accumulation of experience and technical refinements will make these challenging procedures to become a reproducible operative procedure with greater safety.

O-15

Radical Resection of HCC with Massive Tumor Thrombus

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Background: Vascular invasion is one of the poor prognostic factors in hepatocellular carcinoma (HCC). Especially HCC with massive tumor thrombus has a poor prognosis. Radical therapy for HCC with tumor thrombus is limited for resection since both radiofrequency ablation and liver transplantation are contraindicated. However, surgical strategy for HCC with portal vein tumor thrombus (PVTT) and hepatic vein tumor thrombus (HVTT) has not been fully established.

Purpose: To introduce our strategy of aggressive resection for HCC with massive PVTT and HVTT by video presentation.

Methods: Our strategy of the treatment for HCC with massive PVTT and HVTT is that transcatheter arterial chemoembolization (TACE) for the main tumor is performed first (even if the thrombus extends to the main portal trunk), followed by radical surgical resection. Immediate TACE prevents tumor thrombus from rapid progression before resection, confirms no (or few) intrahepatic metastases in the remnant liver, and adds damage to the tumor-bearing liver. Patients may enjoy long-term survival if they receive hepatectomy with preoperative TACE, when the number of primary nodules is no more than two, the portal trunk is not occluded by tumor thrombus, and the indocyanine green retention rate at 15 minutes is better than 20% (Minagawa M, et al. Ann Surg 233: 379–384, 2001). Video presentation: In the following surgical resection, tumor thrombectomy with minimal liver resection preserving portal vein ('peeling-off technique') is performed to avoid postoperative liver failure. The overall survival and the recurrence-free survival rates are comparable with en bloc resection of the portal tumor thrombus (Inoue Y, et al. Surgery 145: 9–19, 2009). In HCC with HVTT, also the thrombus in the inferior vena cava is resected preserving as much caval wall as possible. Extracorporeal circulation is thought to be harmful in the viewpoint of oncology and coagulopathy and is avoided if possible. Indication of resection is also restricted to HCC with HVTT without involving the right atrium.

Conclusion: Preoperative TACE and vein-preserving thrombectomy is safe and effective in HCC with massive tumor thrombus.

O-16

Combination Therapy of Arterial Infusion 5-Fluorouracil and Systemic Interferon-Alpha for Advanced Hepatocellular Carcinoma

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Aim: Hepatic arterial infusion chemotherapy (HAIC) is major treatment modality for advanced hepatocellular carcinoma (HCC) with portal venous invasion (PVI) in Japan. Because of lack of evidence, this modality is not common in the world. The aim of this study is to clarify effectiveness of HAIC.

Methods: Eight hundred and forty five patients with advanced HCC received Peg-IFN alpha 2a (90 µg subcutaneous injection on Days 1 of each week of treatment) and 5-FU (500 mg into hepatic artery on Days 1–5 of the first and second week of each 4-week cycle). The therapy was either terminated at the end of the first cycle in cases with progressive disease, or continued for at least 2 cycles, when responses to treatment were evaluated by RICIST. The survival rate was calculated by Kaplan-Meier method. Predictive factors for survival were calculated by Cox proportional-hazards regression. Predictive factors for effectiveness were calculated by logistic regression.

Results: Of 845 patients, Child-Pugh A/B/C was 477/350/18. Seventy five percent have portal vein invasion and 12% have extra hepatic metastasis. The median survival time was 6.5 months among overall patients. In the Child-Pugh A MST was 8.8 months. CR/PR/SD/PD was 86/188/214/357. MST of the CR was 26.7 months, PR was 12.3, SD was 5.4 and PD was 3.9 months. Predictive factors for survival were T.Bil, Alb, ALT, AFP, DCP, HCV, metastasis and ascites. Predictive factors for effectiveness were PVI, metastasis, ascites, T.Bil, ALT and platelet.

Conclusion: The combination therapy with 5-FU and IFN substantially improved the survival rate among the responders.

O-17

Back Flow Thrombectomy and PIHP for Treatment of Vp4 Multiple Bilobar HCC

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Background: We previously reported the efficacy of dual treatment combining reductive hepatectomy and percutaneous isolated hepatic perfusion (PIHP) for patients with advanced HCC. However these patients are frequently complicated with portal vein tumor thrombus (PVTT) and, in some

cases, deeply sitting PVTT extending into the contralateral portal vein branch (Vp4). Therefore the conventional en bloc resection is not feasible for all patients with extensive PVTT. To overcome this situation, we have developed a unique, simple and safe thrombectomy technique, i.e., back flow thrombectomy technique (BFT). We herein present our treatment results of BFT in combination of PIHP for multiple bilobar HCC with Vp4. (BFT) In case of right hemihepatectomy with Vp4, the portal trunk should be first clamped at the superior border of the pancreas. After transverse venotomy at the origin of the right portal branch, PVTT is extracted by forceps and scissors using suction devices. Of particular note, the vascular clamp at the left first portal branch should be avoided because it crushes PVTT and cause portal obstruction with fragmented tumor thrombus. Instead, back flow portal pressure in the portal system should be kept throughout the thrombectomy procedure. This pressure facilitates extraction of both micro- and macroscopic cancer nests liberated in the blood and reduce the risk of their migration into the future remnant liver.

Methods: Until the end of 2011, 43 multiple bilobar HCC patients with Vp4 underwent reductive hepatectomy with tumor thrombectomy. In 22 of 43 patients, BFT were used. Sixteen of 23 patients had PVTT reaching the contralateral second portal branch. Seventeen of 43 patients were not performed PIHP because of either economical reason, extrahepatic metastases, tumor progression, hepatic dysfunction or infectious complications.

Results: Patency rates of the portal vein in all(43) patients/BFT(22) patients 3 and 6 months after hepatectomy were 92%/90% and 87%/86%, respectively. The median OS of all 43 patients was 14 months and the 1 and 3-year OS rates were 55.5% and 19.1% respectively. In 26 patients who could undergo PIHP as the second treatment, the median OS was 17 months and the 1 and 3-year OS rates were 69.2% and 23.1% respectively.

Conclusions: Tumor thrombectomy by BFT achieved a high rate of portal vein patency 6 months after hepatectomy and expands therapeutic window with PIHP for patients with multiple bilobar HCC and Vp4 PVTT who were previously untreatable. An impressively improved OS achieved by additional PIHP in this situation encourage dual treatment strategy for Vp4 multiple bilobar HCC.

inhibitor of tumor growth and angiogenesis is currently the only approved molecule available in Child A HCC patients with extrahepatic spread and major vascular invasion. This treatment is assessed in an adjuvant setting to prevent recurrence in the remnant liver or in the graft.

Although, few cases of major response or complete remission under sorafenib have been described, there are arguments to consider surgery after down staging with this medical treatment. Since, data on safety of sorafenib administration prior to surgery are lacking, we present the outcome of patients who received preoperative sorafenib.

Sorafenib can be considered in a neoadjuvant setting in 2 situations: (i) to downstage the tumor before liver resection in case of good response, (ii) in a systematic manner in up-front resectable patients, to improve R0 resection rate and decrease postoperative recurrence.

We collected 23 cases of patients who underwent liver resection after sorafenib administration, and compared them to 46 matched patients without prior sorafenib. The drug intake was interrupted at least one week before surgery. Comparison of the sorafenib group with the control group showed that surgical procedure was similar in term of duration (280 vs 240 min) transfusions rates (26 vs 15%) and pedicular clamping (70 vs 74%). Recovery of liver function assessed by prothrombin time (8 vs 72%) and bilirubin level (21 vs 22 μ mol/L) at POD 3 was similar in the two groups. Postoperative morbidity was comparable according to Clavien-Dindo classification. Mortality was nil the sorafenib group versus one (2.1%) in the control group ($p=ns$). This first study assessing the impact of sorafenib before liver resection showed that no adverse effect of sorafenib was observed. A prospective trial (Bioshare) assessing the antitumoral effect of sorafenib in patients with HCC that can be removed by surgery is currently conducted and should display additional results about safety issues of the drug before hepatectomy.

Sorafenib can as well be considered as a bridge treatment to liver transplantation (LT). Although sorafenib could represent an attractive option either alone or in combination with locoregional therapies, only few data are available in the literature. Eleven cases have been published as case reports or as part of a study assessing all types of downstaging therapies before LT; one patient was reoperated for intraperitoneal bleeding and another one was retransplanted for hepatic artery thrombosis. Only one study (Truesdale et al., Transpl Int) collected a series of 10 patients treated with sorafenib prior to LT, and showed a higher rate of acute cellular rejection (67% vs 22%, $p=0.04$) and of biliary complications (OR 12.6, $p=0.03$). In this study, the drug was ceased on the day of transplantation. A prospective trial assessing sorafenib as a bridge to LT is ongoing.

Sorafenib could represent a new tool in the therapeutic arsenal in combination with liver surgery without adverse effect observed after partial resection, while biliary complications have been observed after LT.

O-18

Role of Liver Surgery for HCC in the Era of Targeted Therapy

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Several molecular-targeted therapies (brivanib, bevacizumab, mTOR inhibitors, PI-88...) are being tested and developed in the treatment of HCC. Sorafenib, a multi-kinase

O-19

Current Status of Percutaneous Ablation for HCC

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For more than two decades, hepatic resection has been the most well-established therapy for hepatocellular carcinoma (HCC). As radiofrequency ablation (RFA), introduced in Japan in 1999, produced better survival than percutaneous ethanol injection, RFA is now the first choice among non-surgical treatments for small HCC. Whether RFA is a feasible alternative treatment for HCC smaller than 3 cm remains controversial. Thus, instead of a randomized controlled trial, we conducted a propensity analysis to compare the outcomes of RFA versus surgery.

We perform percutaneous ultrasound-guided RFA under general anesthesia. We initially ablate the feeding artery before the lesion itself to reduce intra-tumoral pressure. This two-step method can easily be performed under pain-free conditions and requires a broad ablation area to minimize the risk of recurrence.

From the initial two-year case analysis, we found tumors with a diameter ≤ 3 cm, regular shape and no prior treatment to be good indications for RFA. After 2002, we selected mainly patients with these favorable characteristics.

From 1999 through 2007, 659 HCC cases with nodules ≤ 5 cm underwent RFA (289 cases) or surgery (370) as the initial curative treatment. Overall and recurrence-free survivals were calculated for all cases, and the propensity analysis was performed thereafter. 1) In all patients, the overall 5-year survival rates after RFA and hepatic resection were 65% and 68%, respectively. The respective recurrence-free survival rates at 5 years were 27% and 26%. Cox proportional hazards analysis revealed no differences between the two groups. However, patient characteristics were different. RFA is more frequently used in cases with poor liver function. Surgery is more frequently used in those with highly malignant tumors. 2) Six factors determining treatment selection were identified using multiple logistic regression analysis. One hundred and forty-six pairs were selected as propensity-score-matched cases. Propensity analysis confirmed that there were no significant differences in either overall or recurrence-free survival between the two groups. 3) Only 0.3% of RFA cases experienced a major complication (bleeding into the abdominal cavity), while 0.5% of surgical cases died due to a surgery-related complication. In conclusion, there was no difference in either overall or recurrence-free survival between patients undergoing RFA and those treated surgically. If appropriate patient selection criteria are applied, RFA under general anesthesia is a safe and effective treatment for small HCC.

O-20

Retrospective Analysis using the Japanese Nationwide Survey for HCC

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Background: Which is better as a therapeutic choice for less advanced hepatocellular carcinoma (HCC) with good liver function between surgery and percutaneous ablation? This has been one of the most important and unsolved problems in hepatology. This retrospective study was conducted to evaluate and compare the therapeutic impacts of surgical resection (SUR), percutaneous ethanol injection (PEI), and radiofrequency ablation (RFA) on long-term outcomes in patients with HCC.

Methods: The Liver Cancer Study Group of Japan started large-scale nationwide survey for HCC in 1965 and has prospectively collected data on patients with HCC in Japan, which was used for this study. Between 2000 and 2005, 28,510 patients with HCC were treated by SUR, PEI, or RFA, among whom we identify 12,968 patients with no more than 3 tumors (3 cm) and liver damage of class A or B. The patients were divided into SUR group (n = 5,361), RFA group (n = 5,548), and PEI group (n = 2,059). Overall survival and time-to-recurrence rates were compared among them.

Results: Median follow-up was 2.16 years. Overall survival rates at 3 and 5 years were respectively 85.3%/71.1% in the SUR group, 81.0%/61.1% in the RFA, and 78.9%/56.3% in the PEI. Time to recurrence at 3 and 5 years were 43.3%/63.8%, 57.2%/71.7%, and 64.3%/76.9%, respectively. On multivariate analysis, the hazard ratio for death was significantly lower in the SUR group than in the RFA (SUR vs. RFA: 0.84, 95% confidence interval, 0.74–0.95; P = 0.006) and the PEI (SUR vs. PEI: 0.75, 0.64–0.86; P = 0.0001). The hazard ratios for recurrence were also lower in the SUR group than in

the RFA (SUR vs. RFA: 0.74, 0.68–0.79; $P = 0.0001$) and the PEI (SUR vs. PEI: 0.59, 0.54–0.65; $P = 0.0001$).

Conclusions: Surgical resection would provide longer overall survival and time-to-recurrence than either RFA or PEI in patients with HCC.

O-21

Local Ablative Therapy versus Partial Hepatectomy for Hepatocellular Carcinoma

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Introduction: Local ablative therapy involves the injection of cytotoxic agents or application of an energy source, resulting in destruction or extirpation of tumor, usually under ultrasound, but occasionally under MRI or CT guidance. The routes of ablation can be percutaneous, laparoscopic or laparotomy.

Of the many forms of local ablative techniques, radiofrequency ablation has evolved as the most accepted and widely practiced local ablative therapy for HCC because of its safety and effectiveness: This is a review comparing percutaneous radiofrequency ablation (PRFA) with partial hepatectomy.

Outcomes: Measures to Compare PRFA and Partial Hepatectomy are:

(1) Overall and Disease Free Survivals

The results of randomized controlled trials and non-randomized comparative studies are controversial to show whether PRFA and partial hepatectomy has similar long-term survivals, or the latter produces better results than PRFA.

The long-term survival results have been shown to be related to whether the tumor is solitary or multiple, and to the size of the lesion. In non-randomized studies, there is a potential bias in patient selection as well.

As the different studies have different inclusion criteria, it is not surprising that the results are controversial.

However, it is reasonable to conclude from the available published data that in well-selected patients (solitary HCC ≤ 3 cm), PRFA produces similar long-term results as partial hepatectomy.

(2) Operative Mortality and Morbidity

From published data, the operative mortality and morbidity are significantly much lower using PRFA than partial hepatectomy.

(3) Health-Related Quality of Life (HRQL)

There is very little data on this aspect. From a non-randomized study carried out in our center using Functional Assessment of Cancer Therapy – Hepatobiliary Questionnaire (FACT-HEP) at baseline, 3, 6, 12, 24 and 36 months after treatment, PRFA produced significantly better scores in HRQL than partial hepatectomy

(4) Other Outcome Measures

These include treatment invasiveness, collateral damage, feasibility (including treatment for patients with liver dysfunctions or multiple HCC), possibility of repeated treatment and limit for the number of treatment for recurrence, PRFA is better than partial hepatectomy.

Conclusion: It is still controversial whether long-term survivals are similar for PRFA and partial hepatectomy. In carefully selected cases (solitary HCC ≤ 3 cm), there is evidence to support PRFA to produce similar long-term survivals as partial hepatectomy.

In many other aspects including treatment mortality/morbidity, health-related quality of life, treatment invasiveness, collateral damage, feasibility, possibility of repeated treatment and limit for the number of treatment for recurrence, PRFA is better than partial hepatectomy.

O-22

Surgical Resection versus Percutaneous Ethanol Injection or Radiofrequency Ablation: Experience from Taiwan

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Hepatocellular carcinoma (HCC) is prevalent in Asia and is the leading cause of death in Taiwan. Resection is the standard curative therapy for early stage of HCC according to various guidelines. Local ablation therapies including percutaneous ethanol injection and radiofrequency were also utilized in treating small HCCs.

A randomized prospective study comparing surgical resection (SR) versus percutaneous ethanol injection (PEI) was performed at National Taiwan University Hospital from year 1998 to 2002. Total 76 patients of HCCs (single or two, with size equal or less than 3 cm, non-cirrhotic or cirrhosis class A or B) were randomized equally. After follow-up period of 12–59 months, recurrence and survival were compared. Recurrence rates are 15/38 in SR group and 18/38 in PEI group, respectively. Five resection patients died of cancer and another three patients died of cancer in PEI group. No statistical significance was found in recurrence and survival between SR and PEI. Tumor size larger than 2 cm and alpha-fetoprotein over 200 ng/ml are correlated with higher recurrence rate.

Another comparative study regarding SR versus radiofrequency ablation (RF) was performed from year 2004 to 2009. Total 100 patients of HCCs (not more than 3 in number and 3 cm in size, non-cirrhotic or cirrhosis class A or B) were randomized equally. After follow-up up to 60 months, recurrence and survival were analyzed. Higher recurrence (28/50) in RF than that (18/50) in SR group was observed, although not statistically significant. Similar survival outcome is also not statistically different between SR and RF group.

For small HCC less than 3 cm, both PEI and RF are comparatively effective as SR. Recurrence is still an important issue after complete treatment of HCCs.

O-23

Radiofrequency Ablation versus Surgical Resection for Small HCC

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Objective: To compare the short-term and long-term outcomes of surgical resection and radiofrequency ablation for the treatment of small hepatocellular carcinoma (HCC) in cirrhotic and non-cirrhotic patients

Summary Background Data: Radiofrequency ablation is a promising, emerging therapy for small HCC. Whether it is as effective as surgical resection for long-term outcomes is still indefinite.

Methods: 2 clinical trials were undertaken.

1. Two hundred thirty HCC patients who met the Milan criteria and were suitable to be treated by either resection or RFA entered into a randomized controlled trial. The primary end point was overall survival; the secondary end points were recurrence-free survival, overall recurrence, and early-stage recurrence.

2. One thousand sixty-one cirrhotic HCC patients were included into a retrospective study. Four hundred thirteen received RFA and six hundred and forty eight received surgical resection. Survival, recurrence-free survival were compared and analyzed.

Results: 1. The 5-year overall survival rates for the RFA group and the resection group were 54.78% and 75.65%, respectively. The corresponding recurrence-free survival rates for the 2 groups were 28.69% and 51.30%, respectively. The 5-year overall recurrence rates were 63.48% for the RFA group and 41.74% for the resection group.

2. The 5-year overall survival and corresponding recurrence-free survival as well as disease-free survival were significantly higher in the surgical resection group compared with the RFA group ($p < 0.001$, $p < 0.001$, $p < 0.001$). In subgroup analyses of solitary HCC ≤ 3 cm, there was no significant difference in RFS between the two groups ($p = 0.719$).

Conclusions: 1. Surgical resection may provide better survival and lower recurrence rates than RFA for patients with HCC to the Milan criteria.

2. When treating Childs A cirrhotics with solitary HCC less than 3 cm, RFA may provide a comparable RFS to surgical resection, but RFA is less invasive.

O-24

A Japanese Nation-Wide Multicenter Randomized Controlled Trial (SURF)

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Which is optimal as a treatment for small HCCs, surgical resection or RFA? Although this has been one of the most important clinical questions in the field of hepatology, it remains unsolved. According to BCLC guidelines, surgical resection is recommended only for those with single tumors without portal hypertension. Liver transplantation and RFA are recommended according to the presence of co-morbidities. In contrast, according to the Japanese guidelines, either resection or ablation is recommended for this subgroup of patients. However, there has not been concrete evidence on which is better. Most of the Japanese surgeons believe in surgery, and recommend surgery. However, hepatologists insist long-term outcome is similar and recommend less invasive RFA. Over the last decade, there have been repeated discussions on this issue in Japan and all agreed that there was a need for more reliable evidence. Supported by Japan Ministry of Health, Labour and Welfare, Japan Surgical Society, the Japan society of Hepatology, we have started a nation-wide multicenter randomized controlled trial (SURF trial) in 2009. So far, 104 centers have joined this study and 213 cases have been registered.

In this presentation, we will summarize the study design and future outlook of the SURF study.

O-25

Gd-EOB-DTPA Enhanced MRI for Hepatocellular Carcinoma: Correlation with Transporter Expression and Implication for Personalized Medicine

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Gd-EOB-DTPA enhanced MRI (EOB-MRI) has proved to be extremely accurate in the detection and characterization of HCCs. To understand the molecular mechanism of EOB-MRI is important for the accurate interpretation of imaging findings and application for personalized treatment. For this purpose, we analysed the molecular background of Gd-EOB-DTPA metabolism in HCCs and obtained the following results.

(1) Hepatobiliary (HB) phase of EOB-MRI is a very sensitive (indirect) molecular imaging for hepatocyte uptake

transporter OATP8 (1B3) expression in HCC cells: The majority of hypervascular HCCs show definite hypointensity on HB phase of EOB-MRI but around 10% hyperintensity. We analyzed the differences in the expression of these transporters by RT-PCR between hypointense and hyperintense HCCs. The grade of OATP8 (1B3) expression was significantly higher in hyperintense HCCs. However, no significant difference was observed in other OATPs. Among export transporters, MRP3 expression was significantly increased in hyperintense HCCs. There is a significant correlation between the grade of OATP8 expression and tumor enhancement ratio on HB phase of EOB-MRI. Hyperintense HCCs more commonly showed moderately differentiated HCC and pseudoglandular pattern. It was considered that in iso- or hyperintense HCCs, a larger amount of Gd-EOB-DTPA would be taken up from the tumor blood sinusoids into HCC cells by OATP8, and be excreted again into tumor blood sinusoids by MRP3 gradually, probably because of the depletion of bile ducts in the HCCs.

(2) OATP8 expression and signal intensity on HB phase of EOB-MRI in hepatocellular nodules significantly decreases during multi-step hepatocarcinogenesis: Semiquantitative analysis of immunohistochemistry revealed that the expression of OATP8 was significantly decreased in accordance with the elevation of the grade of malignancy of the nodules from dysplastic nodule to poorly differentiated HCCs. In addition, OATP8 expression decreased in around 80% of early HCC, resulting in very high detection rate of hypovascular early HCC on HB phase of EOB-MRI.

(3) Hypervascular classic HCC showing hyperintensity on HB phase of EOB-MRI is biologically less aggressive: The differentiation grade was higher and portal vein invasion was less frequent in hyperintense HCC than hypointense HCCs. The percentage of patients showing normal serum levels of AFP, L3 fraction and PIVKA-II in the hyperintense HCCs were higher than those of hypointense HCCs. The patients with hyperintense HCCs showed a significant lower recurrence rate than those with hypointense HCCs. The patients with hyperintense HCCs tended to show longer survival than those with hypointense HCCs. Hyperintense HCCs were considered to be a peculiar subtype of HCC with less aggressive biological nature. Further molecular analysis is now undergoing.

O-26

Intraoperative Ultrasound in Patients with Hepatocellular Carcinoma

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Starting from the end of the '70, intraoperative ultrasound has been introduced and developed to stage the liver disease, and to guide the surgical interventions in patients with hepato-

cellular carcinoma. Without intraoperative ultrasound it would be probably impossible to correctly define the hepatic segments as well as the limits of the tumor, also because of the existing wide variations in the anatomy. More importantly, intraoperative ultrasound allows for three-dimensional reconstruction of the relationships between the tumor, the hepatic veins, and the glissonian pedicles. Such reconstruction is essential for planning the surgical strategy, which should be individualized in each patient with the aim to spare functional liver parenchyma. This work focuses on the role of intraoperative ultrasound to stage the liver disease and to plan the surgical resection, describing the most recent technical achievements.

O-27

Elastography for HCC and Future Liver Surgery

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Background and Aims: Elastography visualizes the elasticity of a soft tissue. If applied to solid organ such as the liver or the pancreas, we can obtain objective findings of stiffness through the elasticity mapping displayed on the monitor or quantified elasticity value. Although intraoperative Ultrasonography (IOUS) is useful for precise intraoperative diagnosis, B-mode IOUS sometimes fails to depict the clear image of small focal liver lesions. Real-time tissue elastography (RTE) can provide clearer contrast than B-mode for such lesions by elasticity of the subject. Shear wave elastography (SWE) can estimate the absolute value of the liver or lesion inside.

Methods: RTE: Between October 2010 and September 2011, intraoperative RTE (IORTE) was performed for 70 hepatocellular carcinomas (HCCs), 54 adenocarcinomas, 19 other malignant tumors (ex. neuroendocrine tumor), 13 benign solid tumors (ex. hemangioma), and 15 liver cysts, after routine B-mode IOUS during hepatectomy. RTE images were classified into six types, from type 1 (even strain) to type 6 (no strain), according to the degree of strain contrast with the surrounding liver [modified elasticity type of liver tumor (mod.ETLT)]. Then, we examined the compliance of RTE for the pathological diagnosis or diagnostic imaging. SWE: We applied SWE to 12 lesions and compared its performance between external and intraoperative application.

Results: IORTE could identify all malignant tumors which were preoperatively diagnosed. Moreover, IORTE detected 9 new lesions which were not detected before. According to RTE images, HCCs were classified as type 3 or type 4 or type 5, with a sensitivity of 83%, a specificity of 60%, and an accuracy of 70%. Meanwhile, adenocarcinomas were classified as type 6, with 68%, 96%, and 86%. Additionally,

benign solid tumors were classified as type 1 or type 2, with 92%, 92%, and 94%. Sixty seven lesions were within 1.5 cm in diameter. Among them, IORTE clearly depicted 13 lesions with obscure contour on B-mode (19%) and 6 undetectable lesions on B-mode (10%) successfully with sufficient contrast. SWE could estimate the stiffness of all 12 lesion when used intraoperatively, despite only 4 lesions were successfully evaluated externally.

Conclusions: IORTE was useful in the differential diagnosis of small focal liver lesions. If combined with CE-IOUS, it could assume a large role in future intra-operative diagnosis. When applied to laparoscopic surgery where finger palpation is abandoned, it may play an important role as ‘virtual palpation’.

O-28

Prospective Assessment of the Indocyanine Green's Camera for the Intraoperative Detection of Subcapsular Primitive and Secondary Liver Tumor

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Introduction: Indocyanine green (ICG) is a vital dye excreted in bile that could be trapped around or into liver tumor. The presence of the dye at the surface of the liver can be detected using an infrared ICG camera. The aim of this prospective study was to evaluate the usefulness of this camera for the intraoperative detection of superficial and/or subcapsular hepatocellular carcinoma (HCC) or liver metastasis (MH).

Material and Methods: Between November 2010 and September 2011, 44 patients (pts) underwent a hepatectomy with diagnosis of HCC (n = 12) or MH (n = 32). After the mobilization of the liver, intraoperative ultrasound and palpation were routinely performed before an exploration of the liver surface with the ICG camera. The surgical strategy impact of this method and histological analysis of resected areas were assessed.

Results: Among pts with MH (n = 32), the camera had identified additional superficial ‘spot’ in 5/32 pts (15%). Resection of these ‘spots’ had changed surgical strategy in all cases and histological analysis diagnosed MH in 3/5 cases. Among pts with HCC (n = 12), additional spots have been demonstrated in 8/12 pts (62%). Resection of these spots had changed surgical strategy in 6/8 pts and malignancy were found in 2/6 cases at histological analysis.

Conclusion: The ICG fluorescent imaging is a technological innovation that increases the sensitivity of the exploration of the liver surface that seems more relevant in liver metastases. The diminution of the size of this camera will create new perspectives in the evaluation of liver surface by laparoscopy.

O-29

Translational Research in Fluorescent Imaging of Liver Cancers: ICG and Novel Agents

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While fluorescent imaging using preoperative intravenous injection of indocyanine green (ICG) has been clinically applied to the real-time identification of liver cancers during hepatectomy, it remains unclear why ICG accumulates in cancerous tissues of hepatocellular carcinoma (HCC) at the time of surgery. Here, we present mechanistic background of ICG-fluorescent imaging of HCC, with some clinical applications of this technique to open and laparoscopic hepatectomy.

In this technique, ICG (0.5 mg/kg) is intravenously injected for a routine liver function test. Intraoperatively, fluorescent images are obtained with commercially-available fluorescent imaging systems. The ICG-fluorescent imaging is useful to identify HCC in real time hepatectomy and to detect grossly unidentifiable HCCs on the resected specimen.

In previous series (170 patients), the ICG-fluorescent imaging identified 277 out of the 280 (99%) microscopically-confirmed HCCs. Among them, 58 out of the 68 well-differentiated HCCs (85%) showed a uniform fluorescence in cancerous tissues, while 18 out of the 23 poorly differentiated HCCs (78%) appeared as rim-fluorescent-type lesions (only the surrounding liver parenchyma showed fluorescence). Among 280 HCCs, 21 nodules (8%) were grossly unidentifiable and detected only by fluorescent imaging on the resected specimen. Microarray analysis on the selected 19 nodules revealed that the ratio of gene expression in cancerous tissue to non-cancerous liver tissue tended to be higher in 13 HCCs with ICG-fluorescence in cancerous tissues than in 6 rim-fluorescent-type HCCs as for Na(+)-dependent taurocholate co-transporting polypeptide (NTCP; median [range], 0.93 [<0.01 –1.75] vs. 0.12 [0.01–0.47], $P = 0.018$), which is associated with portal uptake of ICG by hepatocyte, while no difference was observed in MRP2, which is associated with biliary excretion of ICG [1.02 [0.74–1.83] vs. 0.59 [0.25–1.92], $P = 0.188$]. Such gene expression profiles were also supported by immunohistochemical staining. These results suggest that, in differentiated HCC tissues, portal uptake function is preserved but there exists disordered biliary excretion of ICG probably because of morphologic changes rather than func-

tional changes associated with cancer progression, which allows intraoperative identification of HCC by fluorescent imaging using preoperative intravenous injection of ICG.

More recently, we have developed novel fluorescent imaging technique in order to identify hepatic adenocarcinoma as well as HCC and to evaluate their viability during surgery, through rapid enzymatic reaction between a fluorescent probe and γ -glutamyltranspeptidase, which is often overexpressed on the cell membrane of cancer cells.

O-30

Living Donor Liver Transplantation for Hepatocellular Carcinoma

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The bottle neck of liver transplantation for hepatocellular carcinoma (HCC) is the imbalance between number of candidates and that of organs available. Organ shortage has remains severe, and allocation policymakers are mandated to adopt restriction criteria for the matter of population utility and overall equity. Milan criteria (MC) have been the most influential in this aspect. However, several groups from the East and West have now expanded the MC to some extent (5, 6, or more tumors, while others expanding the maximal size acceptable, to 6.5 cm, 8 cm, or larger). Some have decided to add tumor markers.

At University of Tokyo, we have applied Living donor liver transplantation (LDLT) to HCC exceeding the MC in selected cases. The current guideline for HCC is up to 5 nodules with a maximum diameter of 5 cm (5-5 rule). Until July 2012, 123 patients with HCC underwent LDLT. Of these, 113 (92%) were within Tokyo 5-5 rule criteria and 107 (87%) were within MC. Seventy-seven (63%) presented with hepatitis C virus infection. Overall survival at 3 years and 5 years after transplantation were 81% and 78% (median follow up period 76 months). HCC recurred in 10 patients. Cumulative rates of recurrence at 3 years within and beyond Tokyo 5-5 rule or MC were 7% and 50%, or 8% and 20% ($P = 0.0001$ or $P = 0.13$ by log-rank test, respectively).

As in other studies from Asia, our study, warrants continuing performance of LDLT for HCC exceeding the MC. In regions where organ donation from deceased donor is limited by social and cultural differences, LDLT is widespread as the only realistic option. Under such settings limitations based on the argument of public equity may require flexible adjustments. How much to expand on what grounds in LDLT, deserves further discussions.

O-31

Recent Progress in LDLT for HCC

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In Asia, where the supply of cadaveric grafts remains scarce and the incidence of HCC combined with chronic hepatitis B virus (HBV)- and hepatitis C virus (HCV)-related liver disease is high, adult living donor liver transplantation (LDLT) has been settled upon as a practical alternative to deceased-donor liver transplantation (DDLT). Even in Western countries, where adequate access to DDLT is feasible for HCC patients satisfying the Milan criteria, the necessity for LDLT is well established in particular for more advanced HCC patients who are disadvantaged by current allocation algorithms for grafts from deceased donors due to organ shortage, increasing waiting lists, and the expectation that many patients listed for LT will die while awaiting a suitable organ. In the field of LDLT in Asia, numerous technical innovations were achieved to secure donor safety, as well as to ensure patient survival. The experience with LDLT for HCC has been progressively increasing in many Asian countries to date. Although there are questions regarding the higher recurrence of HCC after LDLT than after DDLT, the application of the Milan and UCSF criteria to LDLT in high-volume multicenter cohorts from Japan and Korea has resulted in patient survival outcomes very similar to those following DDLT. Recently, there have been many progress in LDLT for HCC. Inclusion of biologic tumor markers such as AFP, PIVKA II and PET scan, in addition to parameters of tumor morphology might be the key to establish the best selection criteria of LDLT for HCC. Pretransplantation treatments for HCC to improve posttransplant survival by selecting-out patients whose disease will recur soon or by stopping the progression of tumor are performed by a bridging therapy or by down-staging the tumor.

Intraoperatively 'non-touch isolation/minimal manipulation of tumor' technique is applied to decrease tumor cell dissemination. Management for HCC recurrence after LDLT has evolved by aggressive surgical resection of intrahepatic- and extrahepatic-recurrence. Sorafenib chemotherapy and mammalian target-rapamycin (m TOR) as an immunosuppression are under trials.

O-32

Recommendations for Liver Transplantation for HCC: An International Consensus Conference Report

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While liver transplantation (LT) is widely accepted as treatment for hepatocellular carcinoma (HCC), much controversy remains and there is no generally accepted set of guidelines. An international consensus conference was held on December 2–4, 2010, in Zurich, Switzerland with the aim of reviewing current practice regarding LT in patients with HCC and to develop internationally accepted statements and guidelines. The format of the conference was based on the Danish model. Nineteen working groups of experts prepared evidence-based reviews according to the Oxford classification and drafted recommendations answering nineteen specific questions. An independent jury of nine members was appointed to review the submitted papers and make the final recommendations after debates with the experts and the audience at the conference. This special article presents 37 statements/recommendations covering assessment of candidates for LT, criteria for listing in cirrhotic and non-cirrhotic patients, role of tumour downstaging, management of patients on the waiting list, role of living donation, and posttransplant management.

O-33

Resection vs Liver Transplantation for Resectable HCC

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Liver resection (LR), radiofrequency ablation, and liver transplantation (LT) are recognized as potentially curative treatment for hepatocellular carcinoma (HCC). But the optimal surgical treatment of HCC on well-compensated cirrhosis is controversial.

Although liver transplantation provides the best chance for a cure of HCC due to the complete removal of all carcinogenic liver and can be done even in patients with poor liver function, it is not universally available to all HCC patients because of cadaveric organ shortage and in addition has the increased risks and complexities on the pre-, intra-, and post-operative course of liver transplantation.

By contrast, resection is much more easily and widely available, avoids many of peri-operative risks of liver transplantation and less expensive although the liver function better than Child A is prerequisite for the resection.

And in case of recurrence, transplantation can be done in most cases.

We did retrospective study about 110 LT patients and 303 LR patients from February 1999 to October 2010. We divided patients into 3 groups according to number of risk factors. Recurrence appeared in 25 LT patients (22.7%) and 137 LR patients (45.2%). The recurrence-free survival rates were significantly higher after LT than LR ($p = 0.000$). Five risk factors for recurrence were identified: preoperative alpha-fetoprotein >40 ng/ml, preoperative PIVKA >100 mAU/ml, liver resection, tumor number ≥ 2 cm and positive micro-vascular invasion. Three groups according to number of risk factors showed different recurrence-free survival and overall survival. In the low and intermediate risk group, there was a worse recurrence free survival in those patients who underwent LR compared to those who underwent LT, significantly (low risk; $p = 0.005$, intermediate risk; $p = 0.025$). However, there were no significant differences in overall survival rates between two groups. In the high risk group, there was no significant difference between two groups in recurrence free survival and overall survival rates.

Ho et al reported long-term outcomes after resection versus transplantation for HCC within UCSF Criteria. They reviewed HCC patients who underwent liver resection ($n = 746$) and transplantation ($n = 54$) between 2001 and 2007. Overall survival was similar in the resection and transplantation groups (75.9 and 77.2%, respectively). The recurrence rate in the resection group was higher than that in the transplantation group (65 vs. 34.4%; adjusted hazard ratio, 3.27; range, 1.76–6.08).

Most papers have showed long-term survival rates after liver transplantation and resection were similar, but the latter was associated with a higher recurrence rate. Resection is easier, safer, simpler, and as effective compared with transplantation and therefore is the optimal first choice for patients with high risk patients and old patient with well-compensated cirrhosis.

O-34

VEGF and AFP as Predictors of Survival in Advanced Hepatocellular Carcinoma (HCC) Patients Treated by Sorafenib

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Background and Aims: Alpha-fetoprotein (AFP) response has been reported as a prognostic factor in patients treated with sorafenib, and evaluation of AFP ratios 2 and 4 weeks after starting sorafenib therapy was useful for predicting antitumor response. On the other hand, early elevation of des-γ-carboxy prothrombin (DCP) does not suggest treatment failure by sorafenib. However, AFP value in

one third of the patients receiving sorafenib was not elevated at starting administration. Vascular endothelial growth factor (VEGF) receptor is one of the molecular targets of sorafenib and plasma VEGF has been shown to have an independent prognostic value in patients with HCC. We investigated the prognostic value of changes in plasma VEGF levels and AFP response after sorafenib administration. The antitumor responses were evaluated according to the RECIST criteria 4 weeks after starting sorafenib therapy.

Methods: 63 patients with advanced inoperable HCC were treated with sorafenib. AFP and DCP were measured at baseline, and after 2 and 4 weeks. Plasma VEGF levels were measured before sorafenib administration and every 4 weeks until discontinuation. AFP response was defined as a >20% decrease in AFP during 8 weeks of treatment.

Results: Both 2 and 4 weeks after starting sorafenib therapy, the AFP ratio in the PR + SD group was significantly lower than in the PD group. DCP was elevated in both the PR + SD group and the PD group, 2 and 4 weeks after starting sorafenib therapy. Plasma VEGF increased from baseline within 4 weeks in most patients, however, 68.1% of the patients demonstrated a decrease of plasma VEGF levels within 8 weeks. Patients with VEGF decrease had a longer median survival time than those without. Patients with both VEGF decrease and AFP response showed an uneventful post-treatment course, and those without VEGF decrease and AFP response showed poor survival.

Conclusions: Evaluation of AFP ratios 2 and 4 weeks after starting sorafenib therapy is useful for predicting anti-tumor response, on the other hand, early elevation of DCP does not necessarily suggest treatment failure by sorafenib, as DCP elevation can occur despite therapeutic efficacy. Changes in plasma VEGF levels and AFP response during sorafenib treatment may predict the prognosis of patients with advanced HCC.

O-35

Des-γ -Carboxyprothrombin: The Evaluation on Screening for and Early Diagnosis of HCC in China

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Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths around the world. Asian countries account for 75–80% of the roughly 650,000 HCC cases reported globally each year, of particular note is the fact that China alone accounts for 55% of HCC cases worldwide. The incidence of HCC is on the rise in China, which ranks as the second most common cancer in urban areas and first most common in rural areas. Approxi-

mately 85% of Chinese patients with HCC are infected with the hepatitis B virus (HBV) and approximately 10% of patients are infected with the hepatitis C virus (HCV). Over the past few decades, the screening for and early diagnosis of HCC has attracted attention worldwide, with the purpose of detecting HCC at an earlier stage when curable interventions can be offered to achieve long-term disease-free survival for patients. Several remarkable advances have also been made in the management of HCC in China, but the majority of HCC patients in China still present with advanced stage. Currently, biomarkers – α-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP, also known as prothrombin induced by vitamin K absence-II, PIVKA-II), and lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) – have been recommended to screen for and diagnose HCC by many guidelines worldwide. The combined testing of DCP and AFP or AFP-L3 have been proved to achieve a high level of sensitivity and specificity in detecting HCC, but DCP testing is currently approved only in Japan, South Korea, and Indonesia. At present, ultrasound and AFP measurement at 6-months intervals are the standard tools to screen for HCC in China. AFP is the only serum biomarker that has widely been used to screen for and diagnose HCC in China, and the clinical usefulness of AFP has been confirmed by a randomized controlled trial involving 18,816 patients ages 35–59 with HBV infection or a history of chronic hepatitis. In order to assess the screening and diagnostic value of DCP in Chinese patients with HCC, a large-scale, multi-center study was launched by the Japan-China Joint Team for Medical Research and Cooperation on HCC in 2012. This study found no significant correlation between serum levels of DCP and AFP, DCP may have a specificity as high as 90%, and the combined testing of DCP and AFP have significantly higher sensitivity compared to AFP alone in Chinese patients. This study provides a well perspective that DCP could serve as a biomarker to detect HCC in an early stage and facilitate definitive treatment in Chinese patients. The wide implementation of DCP is expected, especially in China where 55% of HCC cases worldwide live.

O-36

Performance of PIVKA-II in the Diagnosis of Hepatocellular Carcinoma in a Western Cohort of Patients

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PIVKA-II (protein induced by vitamin K absence or antagonist-II) which is routinely used for hepatocellular carcinoma (HCC) in Asian countries is rarely studied in Western countries. We evaluated the diagnostic value of PIVKA-II in a Western series of HCC and assess correlations with clinicopathologic data and prognostic factors of HCC

including microvascular invasion (mVI). Independent open-labeled exploratory study including serum samples of 107 patients with HCC treated by liver resection or transplantation and 37 patients with chronic liver diseases without HCC. PIVKA-II serum level was measured using CLEIA PIVKA-II assay kit (Lumipulse G PIVKA-II, Fujirebio). HCC group included 107 patients (100 men, mean age 56 ± 9 years) with 87% having cirrhosis mainly related to chronic viral infection (58%). Control group was composed of 37 patients (20 men, mean age 56 ± 9 years) with 38% having cirrhosis. HCC mean size was 30 ± 20 mm, with 47% of them being <2 cm. Tumors were multiple in 40% and well-differentiated in 47% of cases. mVI was present in 49 HCC (46%). AFP was higher in HCC than in controls (302 ± 136 ng/ml vs. 9 ± 2 ng/ml, $p = \text{NS}$). PIVKA-II was significantly higher in HCC than in controls (969 ± 218 mAU/ml vs. 18 ± 3 mAU/ml, $p = 0.01$) and significantly higher in poorly-differentiated (1498 ± 398 mAU/ml vs. 401 ± 125 mAU/ml, $p = 0.01$). PIVKA-II was also significantly higher in HCC with mVI than in those without mVI (1683 ± 431 mAU/ml vs. 380 ± 145 mAU/ml, $p = 0.005$). The AUROC curve of PIVKA-II for diagnosis of HCC was 0.91 (95% CI: 0.88–0.94). For prediction of mVI, the AUROC of PIVKA-II was 0.71 (95% CI: 0.61–0.81), respectively. Since mVI was correlated with tumor size, platelets count, PT and PIVKA-II in univariate analysis, we constructed a combined model including these factors that increased the performance for prediction of mVI in HCC diagnosis with an AUROC of 0.80 (95% CI: 0.76–0.84). In conclusion, this study shows the higher performance of PIVKA-II in the non-invasive diagnosis and prognosis of HCC in a western series and its potential for predicting mVI. The mVI predictive model will be validated in an independent prospective study.

O-37

Recent Surgical Strategy for Liver Cancers in the Era of Chemotherapeutic Agents

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The prognosis of patients with unresectable HCC remains poor and the impact of combination systemic chemotherapy including doxorubicin, interferon, cisplatin, and fluorouracil (PIAF) on response and survival are unclear. The purposes of this study was to evaluate the factors associated with response rate, resectability, and survival after cisplatin/interferon α -2b/doxorubicin/5-fluorouracil (PIAF) combination therapy in patients with initially unresectable hepatocellular carcinoma (HCC).

The study included two groups of unresectable patients: those unresectable treated with conventional high-dose PIAF ($n = 84$) between 1994 and 2003 and those selected unre-

sectable without hepatitis or cirrhosis treated with modified PIAF ($n = 33$) between 2003 and 2012. Tolerance of chemotherapy, best radiographic response, rate of conversion to curative surgery, and overall survival were analyzed and compared between the two groups, and multivariate and logistic regression analyses were applied to identify predictors of response and survival.

The modified PIAF group received a higher median number of PIAF cycles (4 vs. 2, $P = .049$), and had a higher objective response rate (36% vs. 15%, $P = .013$), a higher rate of conversion to curative surgery (33% vs. 10%, $P = .004$), and a longer median overall survival (21.3 vs. 10.6 months, $P = .002$).

Multivariate analysis indicated that positive hepatitis B serology (hazard ratio [HR], 1.68; 95% CI, 1.08 to 2.59) and Eastern Cooperative Oncology Group performance status 2 (HR, 1.75; 95% CI 1.04 to 2.93) were independently associated with worse survival while curative surgical resection after PIAF treatment (HR, 0.15; 95% CI, 0.07 to 0.35) was associated with improved survival.

In patients with initially unresectable HCC and no hepatitis or cirrhosis, the modified PIAF regimen is associated with improved response, resectability, and survival.

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O-38

Clinical Practice Guidelines for Management of HCC Western Guidelines

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Clinical practice guidelines are instrumental to provide reliable information about diagnosis and treatment options to physicians, patients and health provider agencies. As a conse-

quence and in order to avoid subjective ideas or wishful thinking about any aspect, all the recommendations in practice guidelines should optimally be based in scientific evidence. There are several systems to grade the strength of scientific evidence and there are internationally accepted documents to design and report diagnostic studies, clinical trials and meta-analysis. As expected, randomized clinical trials are the highest level of evidence if properly designed to define the target population, the sample size and the methodology to treat and follow the patients.

Western guidelines follow this philosophy and scrutinise the reported data according to these standards so that all the recommendations released can be evaluated according to the data used and the degree of strength that those recommendation have reached.

Currently, HCC practice guidelines have been produced by AASLD, EASL, ASCO and ESMO among other scientific associations. In all them, the diagnostic criteria have been homogenised as per the use of dynamic imaging (CT and MRI) and/or biopsy, while patient stratification and treatment allocation is mostly done through the BCLC system.

It is important to note that all Western guidelines emphasize that the documents offer guidance, but for the management of specific patients, the physician in charge of the patient should individualize the evaluation and ultimately, recommend the best approach according to the available resources and his refined assessment of the patient's comorbidities and cultural values.

therapeutic modalities according to patient's health status (ECOG 0–2 or 3–4), liver function (Child-Pugh A/B or C), lymphatic/distal metastasis (yes or no), portal vein invasion (yes or no), tumor number (1, 2–3 or ≥ 4), and size (< 5 cm or ≥ 5 cm, ≤ 3 cm or > 3 cm). The combination of various therapies based on individual disease conditions in HCC patients should be emphasized in clinical practice.

O-40

Clinical Practice Guidelines for Management of HCC in Korea

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Hepatocellular carcinoma (HCC) is one of the most common malignancy in Korea, with more than 10,000 new cases annually. Despite substantial progress in the diagnosis and treatment of HCC, the prognosis of HCC is still dismal particularly in advanced diseases. Several regional guidelines including the United States, Europe, and Japan were made based on the evidences for optimal management of HCC. However, due to different medical system and available resources among nations, it is hard for one guideline the gold standard in the world. The Korean Liver Cancer Study Group (KLCSG) and the National Cancer Center (NCC), Korea jointly produced the Clinical Practice Guidelines for HCC for the first time in Korea in 2003. As more national and foreign data are accumulated, Korea recently revised the guidelines in 2009.

Regarding HCC diagnosis, typical finding of HCC in either one of dynamic contrast enhancement CT or MRI is enough for the diagnosis, regardless of serum AFP level, if a cirrhotic patient has a tumor ≥ 2 cm. In a liver nodule small than 2 cm, one typical dynamic imaging pattern is necessary if AFP ≥ 200 ng/ml, and two typical imaging patterns are necessary if AFP < 200 ng/ml.

As an initial evaluation, ICG-R15, bone scan, chest CT scan, angiography, PET-CT scan, gastroscopy can be done. Based on the tumor burden, liver function, and performance status, curative treatments such as resection, liver transplantation, radiofrequency ablation (RFA), and ethanol injection can be applied. Noncurative treatments consist of transarterial chemoembolization (TACE), radiotherapy, and systemic chemotherapy (sorafenib or cytotoxic chemotherapy). Other therapies including drug eluting bead TACE, Yttrium-90 radioembolization, high-intensity focused ultrasound (HIFU), hepatic arterial infusion chemotherapy (HAIC), and metastasectomy are classified into clinical trials.

Although the best candidate for resection is single small HCC with Child-Pugh A and no portal hypertension, Korean guidelines suggest that limited resection might be possible in a patient with Child-Pugh score 7 and mild portal hypertension (and slight bilirubin elevation). As in AASLD guide-

O-39

Treatment Algorithm for HCC in China

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Primary liver cancer (PLC) is a most common malignancy, and more than half of these cases, of which hepatocellular carcinoma (HCC) accounts for about 90%, are estimated to occur in China. PLC is the second cause of cancer deaths in China. The key problems for HCC treatment in Chinese patients are severe cirrhosis, portal vein invasion, distant metastasis, low resectability and high recurrence rate. The management of HCC should be carefully schemed according to patients' general condition, liver compensation, distal metastasis, vascular invasion, in addition to tumor size, number and involvement. Hepatectomy, liver transplantation, local ablation, transarterial chemoembolization (TACE), radiotherapy, systemic therapy including molecular targeted therapy with sorafenib etc., as well as traditional Chinese medicine and supportive care are applied in different stages of HCC patients. The clinical guideline for management of HCC has recently been approved by the Ministry of Health in China. An algorithm for HCC treatment is proposed for selection of

lines, Korean guidelines state that alcohol injection and RFA are equally effective for tumors < 2 cm. However, the necrotic effect of RFA is more predictable in all tumor sizes and in addition, its efficacy is clearly superior to that of alcohol injection in larger tumors.

The main indication of TACE is HCC without main portal vein invasion or extrahepatic metastasis. However, superselective TACE can be applied even in HCC with portal vein thrombosis if a patient has acceptable liver function and HCC burden is small. It is unique that Korean guidelines recommend ethanol injection, RFA or radiation therapy combined with TACE if it is anticipated that anti-tumor effect is unsatisfactory with TACE alone.

Sorafenib could be used in HCC with Child-Pugh A (or high B) and good performance when the patient has extrahepatic metastasis or does not respond to other treatment. Systemic cytotoxic chemotherapy can also be considered, but has low evidence level.

External radiation therapy is one option in Korean guidelines, so it can be applied in HCC patients with Child-Pugh A (or high B) if HCC burden is less than 2/3 of liver volume. Radiation therapy is also the modality for the treatment of portal vein tumor thrombosis.

O-41

Japanese Guidelines

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Against hepatocellular carcinoma (HCC), three therapeutic choices are currently recognized as effective: surgery, including liver resection and liver transplantation, percutaneous ablation therapy as represented by radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE). Both liver function and tumor conditions must be taken into consideration to choose one among the three choices, because a HCC carrying patient usually has chronic liver damage. Thus, treatment selection is difficult and complicated.

The Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan were devised to allow the attending physician and the patient to easily select evidence-based care among the above effective choices. Now the second version is available, which were published in 2009. The essential features of the Japanese Guidelines have been summarized in two figures, one for a hepatocellular carcinoma surveillance algorithm and the other for a hepatocellular carcinoma

treatment algorithm. Especially, the algorithm related to the treatment of HCC has been simplified based on three factors: degree of liver damage, number of tumors, and tumor diameter. The treatment methods that are recommended have been narrowed down to one or two. Now this treatment algorithm is widely accepted in Japan as useful to explain the complex decision-making process to patients.

One of the distinguished differences between the Japanese and the Western guidelines is the position of surgical resection. The Japanese guidelines recommend that resection for HCC with good or slightly injured liver function (liver damage A or B) and 3 or fewer tumors, whereas the indication of resection is extremely limited to a single and small HCC (<2 cm in diameter) with normal liver function in the Western guidelines. Of course, the long-term survival after resection for multiple HCCs (58% at 5 years) was much better than that for a single HCC, however, this does not mean contraindication of resection for multiple HCCs, because no other treatment choice can achieve such a good survival. In spite of no strong evidence available, RCT to compare the clinical significance of resection to other non-surgical treatments is not acceptable, because of the overwhelming impact of resection on survival. We are now revising the third version of the Japanese guidelines, which will be also constructed based on not only RCT-derived evidence, but also clinically important knowledge and experiences.

O-42

Peretinoin, Acyclic Retinoid, Prevents the Recurrence of HCC after Curative Treatment: Results of a Phase II / III Randomized Placebo-Controlled Trial

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Hepatocellular carcinoma (HCC) is a poor prognosis cancer leading to death, with high rate of recurrence after curative therapy. The three-year recurrence rate is pretty high such as 50% in the general population, and more than 70% in hepatitis C-positive patients. No effective therapy for HCC recurrence has been established. It is known that retinoid may play a role of inhibition of tumor growth. Peretinoin is a synthetic retinoid with retinoic acid receptor and retinoid X receptor agonist activity. After phase I study evaluating safety dose, we started a multicenter, randomized, double-blind, placebo-controlled study. A total of 401 HCV positive patients were randomized to receive one of the following regimens: peretinoin 600 mg/day, peretinoin 300 mg/day, or placebo for up to 96 weeks. The primary endpoint was recurrence-free survival. The recurrence-free survival rates in the peretinoin 600 mg group, the peretinoin 300 mg group, and the placebo group were 71.9%, 63.6% and 66.0% at one year; 43.7%,

24.9%, and 29.3% at three years, respectively. The dose-response relationship based on the hypothesis of ‘efficacy begins to increase at 600 mg’ was significant ($p=0.023$). Furthermore, the recurrence-free survival was significantly higher in the group of Child-Pugh A and less 2 cm in size of tumor in the 600 mg group. Although adverse events increased with peretinoin dose, adverse events over grade 2 were not observed. In conclusion, Peretinoin will be a novel first-line agent to reduce recurrence of HCC.

O-43

The Role of Interferon Therapy for the Treatment of Hepatitis C Virus-Related Hepatocellular Carcinoma

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The outcome after curative resection for hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) is still unsatisfactory because of the high rate of recurrence of HCC including intrahepatic metastasis originating from the primary carcinoma and multicentric carcinogenesis after surgery.

The multicentric carcinogenesis after surgery is affected by persistent active hepatitis and hepatic fibrosis caused by chronic hepatitis C.

It is well known that interferon (IFN) therapy suppresses the development of HCC, and improves liver function and histology in patients with chronic hepatitis C. The prognosis after resection of HCV-related HCC was significantly better in patients in whom HCC was detected after IFN therapy than in those who did not undergo IFN therapy previously. Many studies including our randomized clinical trial shows that IFN therapy decreases HCC recurrence after curative resection of HCV-related HCC. The suppressive effects of IFN therapy on HCC recurrence appeared to be stronger in patients who showed a sustained viral response. In addition, IFN therapy preserves or improves the liver function in patients with HCV-related HCC. Thus, IFN therapy increase survival after curative resection of HCV-related HCC not only by preventing HCC recurrence but also by improving liver function and increasing the likelihood of patients being able to undergo radical treatment for HCC recurrence, when treatment is successful. Recently, low-dose intermittent IFN therapy has also been reported to be effective in suppressing HCC recurrence.

Not only treatment for HCC but also treatment for HCV including IFN therapy is important in the management of patients with HCV-related HCC.

O-44

Vitamin K and Recurrence of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the major malignancies worldwide, claiming more than 30,000 victims in Japan each year. Due to the prevalence of regular surveillance for HCC in highrisk group, HCC is detected in not a few patients while they can receive potentially curative treatment such as surgical resection and radiofrequency ablation. Nevertheless, the long-term prognosis of HCC is not favorable, primarily due to frequent recurrence even after curative treatment. Thus, prevention of HCC recurrence has clinical top priority.

Vitamin K2 has been used for osteoporosis and its safety has been confirmed. A couple of small-sized clinical studies reported that HCC recurrence was prevented by the administration of vitamin K2. Thus, this multicenter double-blind randomized placebo-controlled trial was conducted.

Candidate participants were those who had received curative resection or ablation for primary HCC or first intrahepatic recurrence. After screening for inclusion and exclusion criteria, patients were randomly assigned to receive placebo, 45 mg/day, or 90 mg/day vitamin K2. HCC recurrence was surveyed every 12 weeks with dynamic CT or MRI, which was finally judged by an independent review committee, with HCC-specific tumor markers monitored every 4 weeks. The primary aim was to confirm the superiority of active drug to placebo concerning disease-free survival, and the secondary aim was to evaluate dose-response relationships. Hazard ratios (HRs) for disease occurrence and death were calculated using a Cox proportional hazards model.

Disease-free survival was assessed in 548 patients, including 181 in the placebo group, 182 in the 45-mg/day group, and 185 in the 90-mg/day group. Disease occurrence or death was diagnosed in 58, 52, and 76 patients in the respective groups. The prescheduled second interim analysis, planned when 160 events were recorded, indicated that vitamin K2 did not prevent disease occurrence or death, with an HR of 1.150 (95% confidence interval: 0.843–1.570, $P = 0.811$) between the placebo and combined active-drug groups, and the study was discontinued. There was no significant difference in the incidence of any adverse event between the placebo and active-drug groups.

O-45

Preventing HCC Recurrence: Perspectives in the Modern Era of Antiviral and Targeted Therapies

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The annual recurrence rate after curative treatment of HCC is as high as 10–15%. Adjuvant therapies, including chemotherapy, biologic therapy, immunotherapy, antiviral therapy, as well as TACE and HAIC, have all been enthusiastically tried, in a hope to minimize the recurrence rate.

However, no measure has yet been accepted as a therapeutic guideline.

Conventional interferon (IFN) has been most heavily tested, and a beneficial effect was identified in several meta-analyses. However, a recent multi-center, prospective trial from Taiwan found no effect of conventional IFN in reducing the recurrence rate of either HBV- or HCV-related HCC.

With the rapid advancement of anti-HCV and anti-HBV therapy, conventional IFN therapy alone does not seem to be an ideal choice for adjuvant therapy. Recent evidence has suggested a better efficacy of PEG-IFN plus ribavirin on reducing recurrence of HCV-related HCC. Furthermore, addition of protease inhibitors into above combination appeared to hold even better promise in HCV-related HCC. Similarly, a recent nation-wide cohort study in Taiwan has uncovered that nucleoside analogue use is associated with a lower risk of HCC recurrence among patients with HBV-related HCC after liver resection.

Sorafenib, a molecular-targeted therapy (MTT), has become standard therapy for advanced HCC. Along this line, many MTT have been under randomized control trials for evaluation of their efficacy in preventing HCC recurrence.

In summary, in the modern era of antiviral and targeted therapies, new approaches for the prevention of HCC recurrence are expected to shed new light on this field.

Poster Presentations

P-1

Surgical Treatment of Hepatocellular Carcinoma Associated with the Metabolic Syndrome

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Objective: The incidence of metabolic syndrome associated hepatocellular carcinoma (MS-HCC) is increasing. However, the results following liver resection in this context are poorly described.

Patients and Methods: All resected patients with MS as unique risk factor for HCC who underwent liver resection between 2000 and 2011 were retrieved retrospectively from an institutional database. Pathological analysis of the underlying parenchyma took into account fibrosis and non-alcoholic fatty liver disease activity score (NAS). Patients were classified as having normal (absence of severe fibrosis and NAS < 2) or abnormal (either severe underlying fibrosis or without severe underlying fibrosis, but with a NAS ≥ 2) underlying parenchyma. Their characteristics and outcomes were compared.

Results: A total of 560 resections for HCC were performed during the study period. Sixty-two (age 70 years, range 50–84) patients with MS underwent curative hepatectomy for HCC, including 32 (52%) major resections. Normal underlying parenchyma was present in 24 (31%) patients. The proportion of resected HCCs labeled as MS-HCC continuously grew during the study period from 2.5% in 2000 reaching more than 15% of the whole HCC population in recent years. Mortality and major morbidity rates were 11% and 58% respectively. Compared to patients with normal underlying liver, patients with abnormal liver had increased mortality (0% vs. 18%, $p = 0.026$) and major complications (12% vs. 42%, $p = 0.01$) including liver specific (25% vs. 0%, $p = 0.009$) as well as cardio-respiratory complications (45% vs. 12.5%, $p = 0.016$). In multivariable analysis, a non-severely fibrotic yet abnormal underlying parenchyma was a risk factor for major complications (HR: 5.656; CI: 1.206–26.523; $p = 0.028$). Three-years overall and disease-free survival rates were 75% and 70% respectively and were not influenced by the underlying parenchyma.

Conclusions: HCC in patients with metabolic syndrome becomes more and more common. Liver resection is appropriate but carries a high risk even in the absence of severe fibrosis. Refinements in peri-operative management of these patients are needed.

P-2

The Impact of Posthepatectomy Liver Failure on the Recurrence of Hepatocellular Carcinoma and Prognosis

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Background: Patients with hepatocellular carcinoma (HCC) who underwent hepatectomy highly developed an intrahepatic recurrence, even though it was a curative one. The relationship between liver injury and the recurrence of HCC has not been described. This study evaluated whether posthepatectomy liver failure, as defined by the International Study Group of Liver Surgery (ISGLS), affected the recurrence of HCC and prognosis.

Methods: We performed a retrospective cohort study that enrolled 287 patients with HCC who underwent hepatectomy between 2006 and 2010 at Kyoto university hospital. Early posthepatectomy liver failure (EPLF) was defined as liver failure occurring between postoperative days 5 and 10. The patients were divided into an EPLF group and non-EPLF group according to the presence or absence, respectively, of EPLF. Disease-free survival (DFS) and overall survival (OS) were compared between these 2 groups. The influences of host-related, surgery-related, or tumor-related factors on the outcomes were evaluated in multivariate analyses.

Results: The EPLF group and non-EPLF group contained 89 and 198 patients. The probability of DFS and OS were statistically increased in non-EPLF group, compared to EPLF group (DFS; HR [95%CI]: 1.63 [1.18–2.22], $P = 0.0021$, OS; HR [95%CI]: 1.78 [1.06–2.94], $P = 0.033$). In the multivariate analyses of DFS and OS, the HRs [95%CI] were 1.48 [1.06–2.06] and 1.85 [1.08–3.12], respectively. EPLF was an independent factor for both DFS and OS.

Conclusions: EPLF was associated with postoperative HCC recurrence and poor survival. The prevention of EPLF might contribute to the improved prognosis of patients with HCC.

P-3

Duration of Hepatic Vascular Inflow Clamping and Survival after Liver Resection for Hepatocellular Carcinoma

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Background: Several clinical factors, such as the level of α -fetoprotein (AFP) or of protein induced by vitamin K absence or antagonist (PIVKA) II, viral infection and intraoperative bleeding, have been reported to be predictive of postoperative survival in patients with hepatocellular carcinoma (HCC) undergoing liver resection. Especially, recent reports have shown that intraoperative bleeding can predict tumor recurrence and patient survival following hepatectomy for HCC. However, few previous investigations have addressed the influence of the Pringle manoeuvre on postoperative survival after HCC surgery. Because the Pringle manoeuvre is performed during liver resection to control intraoperative bleeding, it might be more predictive of postoperative survival than intraoperative blood loss in patients undergoing surgery for HCC.

Objective: The aim of this study was to evaluate the influence of the duration of hepatic vascular inflow clamping (Pringle time) on the survival of patients with any type of liver background (not only cirrhosis) undergoing liver resection for HCC.

Methods: Patients who underwent liver resection between April and December 2008 for HCC using the Pringle manoeuvre were identified retrospectively from an institutional database and divided into two groups: group 1 had a Pringle time of 60 min or less, and group 2 a Pringle time of more than 60 min. Univariable and multivariable analyses were performed to identify predictors of postoperative survival. Kaplan-Meier analysis was used to compare overall survival between the groups.

Results: A total of 357 patients were enrolled; 242 patients had a Pringle time of 60 min or less (group 1), and 115 patients had a Pringle time of more than 60 min (group 2). Patients in group 2 had a shorter overall survival than those in group 1 ($P = 0.010$). Univariable analyses showed that type of HCC (primary versus recurrent), maximum tumour diameter, hepatic venous infiltration, platelet count, serum PIVKA II level, blood loss (700 ml or less versus more than 700 ml), duration of operation (300 min or less versus more than 300 min) and Pringle time (60 min or less versus more than 60 min) were predictive of postoperative survival. Multivariable analysis indicated that only Pringle time was associated with postoperative survival (odds ratio 1.83, 95 per cent confidence interval 1.08 to 3.10; $P = 0.024$).

Conclusion: Longer Pringle time is an important predictor of shorter postoperative survival in patients undergoing liver resection for HCC.

P-4

Outcomes of Liver Resection for Hepatocellular Carcinoma with Thrombocytopenia

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Aims: To elucidate the surgical outcomes for patients with thrombocytopenia who undergo liver resection according to Makuuchi criteria for treatment of hepatocellular carcinoma (HCC).

Methods: The clinical characteristics and outcomes of 448 HCC patients who had undergone elective liver resection were retrospectively analyzed. The patients were classified into a thrombocytopenia group (n = 100) and a without-thrombocytopenia group (n = 348) according to whether their platelet count had been <100,000/ml at the time of surgery.

Results: The thrombocytopenia group experienced worse preoperative liver function compared to the without-thrombocytopenia group, as assessed by albumin level (3.6 vs. 3.9 g/dl, respectively; $p < 0.0001$), total bilirubin level (0.76 vs. 0.62 mg/dl, respectively; $p < 0.0001$), prothrombin rate (91% vs. 100%, respectively; $p < 0.0001$), and ICGR15 rate (18% vs. 11%; $p < 0.0001$). The median maximum tumor diameter of the thrombocytopenia group was significantly smaller (2.8 cm vs. 3.5 cm, respectively; $p < 0.0001$). The thrombocytopenia groups showed similar surgical outcomes in terms of surgical time (353 vs. 354 min, respectively; $p = 0.73$), Pringle time (106 vs. 111 min, respectively; $p = 0.19$), and blood loss volume (382 vs. 326 ml, respectively; $p = 0.07$); complication rate in terms of Clavien grade ($p = 0.07$); 5-year overall survival rate; (58.3% vs. 56.5%, respectively; $p = 0.14$); and 5-year recurrence-free survival rate (12.9% vs. 23.0%, respectively; $p = 0.61$).

Conclusions: Liver resection can provide beneficial short- and long-term outcomes for HCC patients with thrombocytopenia.

quency ablation(RFA) for HCC in segment 6 of the liver in 2004. He underwent RFA for recurrence HCC in segment 5 of the liver in 2007. And he underwent RFA for recurrence HCC in segment 7 of the liver 2011. After that, a tumor marker, PIVKA-II elevated to 79 in 2011, recurrence tumors were detected on CT in 2012. CT shows a tumor in segment 7 and 8, 58 mm in diameter. It's border is irregular and enhanced in arterial phase and portal phase and washed out in delayed phase. Several tumors with about 20 mm in diameter, have the similar contrast effect were detected at around it. Further, CT shows tumors in segment 8 and segment 1 of the liver, 38 mm and 26 mm in diameter, respectively. The tumor in segment 8 non-uniformly enhanced in arterial phase and the tumor in segment 1 uniformly enhanced in arterial phase, and both tumors washed out in delayed phase. Other than those, swollen lymph nodes around pancreatic head, para-aortic artery, and esophagus hiatus site were detected on CT. MRI shows all of the tumors were low intensity ambiguous boundary tumors in T1 weighted images, and high intensity tumors in T2 weighted images. And EOB-MRI shows uptake of EOB were reduced in all of the tumors in hepatobiliary phase. However, uptake of EOB was observed in only a segment 8 tumor in hepatobiliary phase. In terms of hepatic function values, ICG-R15 was 12% and liver damage is A. And tumor markers, AFP, PIVKA-II, CEA and CA19-9 were 5, 364, 2.3 and 2 respectively. Based on the diagnosis of suspicion of intrahepatic cholangiocarcinoma or mixed type hepatocellular carcinoma, we performed right hepatectomy and diaphragm resection. And he was discharged on the 17th postoperative day in good postoperative course. Pathological findings were hard white several tumors with irregular border without capsule and one elastic soft green tumor with capsule in segment 8. The former was a poorly differentiated adenocarcinoma containing a lot of fibrillary elements with portal and venous infiltration. The latter was a moderately differentiated hepatocellular carcinoma with Hep1 positive and Gly3 negative. Based on these results, the tumors were diagnosed as a double cancer of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. As far as we search for reported cases of double cancer of hepatocellular carcinoma and intrahepatic cholangiocarcinoma, this case was found to be precious one. So we experienced this time a case with double cancer of hepatocellular carcinoma and intrahepatic cholangiocarcinoma which were developed after RFA, we report the result with certain consideration.

P-5

A Case with Double Cancer of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Observed after Radiofrequency Ablation

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The patient is a 69 year-old man. He was diagnosed alcoholic liver dysfunction in April 2004. Then hepatocellular carcinoma(HCC) was detected. So he underwent radiofre-

P-6

A Case of Combined Hepatocellular-Cholangiocarcinoma with Stem-Cell Features

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Background: Combined hepatocellular-cholangiocarcinoma (HCC and CCC) is rare type of tumor, comprises about less than 1% of all liver carcinomas. Liver cancer from stem-cell origin has been reported as a new entity, but the clinical features have not been fully understood. Here, we report a case of resected combined hepatocellular-cholangiocarcinoma with stem-cell features.

Case: A 68 year old-woman was pointed out two liver tumors by computed tomography (CT) during the followed up of her hepatitis C. Tumor in S2, 2 cm in diameter, showed early enhancement in the arterial phase and washed out in the late phase of CT images. Tumor in S8, 4.8 cm in diameter, showed early enhancement with not stained area in the arterial phase, and washed out in the late phase of CT images. Portal tumor thrombosis was detected in P8 ventral branch. These tumors showed low intensity in the hepatobiliary phase of magnetic resonance imaging with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid. Therefore, we diagnosed tumors in S2 was classical HCC, and tumor in S8 had a possibility of combined HCC and CCC. ICG retention rate 15 minutes (ICGR15%) was 20.1%. Her blood platelet count was 56000/ul because of aplastic anemia. No serum tumor markers were elevated.

Result: We performed S8 sectionectomy and partial resection of S2. Postoperative course was uneventful, and she discharged our hospital on the 9 postoperative days. Cut surface shows yellowish soft simple nodular tumor in S2, and white hard simple nodular tumor with extranodular growth in S8. Pathological diagnosis of tumor in S2 was typical well differentiated HCC with sever fatty change. Meanwhile, tumor in S8 revealed that tumor cell with oval-shaped nucleus arranged in alveolar or cord-like structure.

According to the immunostaining, there were negative for CK7, CD56, C-KIT and CEA, and positive for CD10. Due to these findings, pathological diagnosis of tumor in S8 was combined HCC and CCC with stem-cell features, intermediate-cell subtype. Pathological diagnosis was T4 (multiple, 48 mm, vp2), N0, M0, Stage4A.

Conclusion: Combined hepatocellular-cholangiocarcinoma has the possibility of stem-cell origin.

P-7

Simultaneous Identification of Two Liver Cancers After Resection of Colon Cancer

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We encountered a chronic hepatitis C patient in whom early colon cancer and 2 liver masses were found simultaneously, and the differentiation of the liver tumors was difficult. Herein, we report the case. The patient was a 71-year-old man with colon cancer that was found during follow-up for hepatitis C, and he underwent endoscopic resection in July 2010. At the same time, 2 masses were detected in the liver on CT. A mass stained intensely in the S7 region was diagnosed as hepatocellular carcinoma, and another mass that was enhanced heterogeneously in the S6 region was suspected as colonic metastasis to the liver or intrahepatic cholangiocellular carcinoma. Hepatectomy was performed in September 2010. On histopathological examination, the former was found to be a moderately-differentiated hepatocellular carcinoma (HCC). The latter was a moderately-differentiated adenocarcinoma that was positive for cytokeratin (CK) 7 and negative for CK20 on immunostaining, upon which intrahepatic cholangiocellular carcinoma was diagnosed. For the differentiation of liver tumors in cases of colon cancer, immunohistological diagnosis using the CK profile is useful.

P-8

Management of Small Hepatocellular Carcinoma by High Intensity Focused Ultrasound Ablation in Patients with Cirrhosis – An Eastern Experience

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Background: For most patients with small HCC hepatectomy or liver transplantation is widely accepted as a good choice of treatment. However, local ablation therapy provides a very good alternative for those who does not want or cannot tolerate a major surgical procedure. High-intensity focused ultrasound (HIFU) ablation is a non-invasive treatment for hepatocellular carcinoma (HCC). However data on long term follow up is restricted. In this study we aim to analysis the outcome for patients receiving this treatment.

Patients and Method: From Oct 2006 to Sept 2010, 1321 patients were diagnosed HCC. 457 patients received surgical interventions. The clinical data were recorded prospectively in a computerized database by a single research assistant. Total 112 patients received HIFU as a treatment of HCC in Department of Surgery Queen Mary Hospital. Amongst these patients, 47 patients has HCC smaller than 3 cm. 59 patient receiving percutaneous radiofrequency ablation were selected for comparison. Preoperative variables of these patients were compared. Perioperative data and survival analysis was also compared.

Results: There were forty seven patients received HIFU therapy during this period. Total fifty two tumours were ablated by this treatment entity. The median age for the patients was 62 (range 34 years–84 years). The median tumour size was 1.5 cm (range 0.8–2.7 cm). Forty-two patients (89.4%) had one tumour on presentation. Five patients (10.6%) had two tumours on presentation. Fifty-nine patients received percutaneous RFA during this peroid. Total Sixty five tumours were ablated by this method. The median age for the patients was 60 (range 23 years–83 years). The median tumour size was 1.9 cm (range 1.0–2.8 cm). Fifty-two patients (88.1%) had one tumour on presentation. Six patients (10.2%) had two tumours on presentation. There is sixteen patients (34%) in Child Pugh B cirrhosis in the HIFU group while there was only five patients (8.5%) in Child Pugh B cirrhosis in the RFA group ($p = 0.001$). No statistical significant difference for Clavein-Dindo grade IIIA or above complications between these two groups were observed. In the HIFU group, the one year survival was 97.4% and the three year survival was 81.2%. In the RFA group, the one year survival was 94.6% and 79.8%. ($p = 0.53$). In the HIFU group the one year disease free survival was 63.6% and the three year disease free survival was 25.9%. In the RFA group the one year disease free survival was 62.4% and the three year disease free survival was 34.1% ($p = 0.683$).

P-9

Laparoscopic Left Lateral Sectionectomy Using Staplers – Standardized Technique and Results

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Background: Laparoscopic liver resection remains limited to a relatively small number of institutions because of insufficient hepatic and laparoscopic surgical experience and few training opportunities. The aim of this study was to assess the feasibility and safety of an improved laparoscopic left lateral sectionectomy technique using staplers.

Methods: At Iwate Medical University Hospital, 24 patients underwent pure laparoscopic left lateral sectionectomies (LLLS). In 2008, the LLLS procedure was standardized at this institution, and 16 of the 24 patients underwent this operation according to the revised procedure. The standardized procedure is characterized by the absence of the Pringle maneuver; traction of the round ligament with Endoloop®; minimal liver parenchymal transection without exposure of the portal pedicles or hepatic vein; and the use of linear staplers to divide the portal pedicles or hepatic vein.

Results: The overall median surgical time was 108.5 min (range: 85–210 min), and the median blood loss was 10 mL (2–430 mL). The surgical time was significantly shorter after the procedure was standardized in 2008 than it was prior to standardization (105 min vs. 153 min, $P < 0.001$). There was also significant difference in the blood loss between surgeries performed before 2008 and those performed after 2008 (23 mL vs. 10 mL, $P < 0.05$). One patient required conversion from LLLS to open laparotomy because of a left hepatic vein injury during mobilization of the liver. There was only 1 postoperative complication: a Clavien-Dindo classification grade IIIa wound infection. No patient mortalities occurred.

Conclusions: A standardized LLLS procedure using staplers has been established and demonstrated to be both safe and feasible.

P-10

Rt. Hemihepatectomy for Huge Hepatocellular Carcinoma

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Objective: To evaluate our surgical strategy of Rt. hemihepatectomy for huge hepatocellular carcinoma (HCC).

Background: Anterior approach and Liver hanging maneuver were developed to avoid tumor dissemination and serious complications during liver mobilization. However, it is sometimes very complicated and hazardous to use these techniques for huge HCC with severe compression of inferior vena cava (IVC) or hepatic hilum. And the risk of intrahepatic recurrence after curative resection of huge HCC is markedly high. Therefore an oncological meaning of Non-touch technique for huge HCC is still unclear.

Methods: From January 2004 to December 2012, a total of 402 consecutive patients were diagnosed with HCC and received hepatectomy. Among them, 43 patients underwent Rt. hemihepatectomy with huge HCC (over 10 cm in diameter). In this series of patients, clinical data and surgical outcome were analyzed retrospectively.

Surgical Techniques: It is very important to avoid intraoperative tumor rupture and uncontrollable hemorrhage from huge tumor. Therefore, for the first step, liver hilar dissection was performed to resect Rt. hepatic artery and

portal vein. For the next step, during mobilization of the liver, a devascularization of tumor feeder vessels from diaphragm was carefully performed. After complete mobilization of the liver from IVC, ultrasound aspiration dissector was used for parenchymal transection. Belghiti's hanging tape was used to control bleeding in the deeper parenchymal plane.

Results: R0 operation was performed in 29 cases. Fourteen patients received reduction surgery and postoperative chemotherapy. Complete mobilization of the liver was feasible in all patients. Mean operation time was 615 min (286–1088 min). Mean volume of intraoperative blood loss was 2045 ml (405–6650 ml). Thoracotomy was added only in 2 cases. In 3 cases (7.0%) with diaphragm invasion from HCC, a diaphragm resection was performed. In 18 cases (41.9%) with portal vein thrombus (Vp3 Vp4), thrombectomy were feasible. IVC of most patients (40 cases 93.0%) were severely compressed. Three patients (7.0%) were diagnosed as a HCC with IVC thrombosis (Vv3) and received thrombectomy. Uncontrollable hemorrhage due to injury of IVC was not occurred. There was no hospital mortality. The 3 most common complications were bile fistula (3 cases 7.0%), wound infection (3 cases 7.0%) and massive ascites (2 cases 4.6%). Peritoneal dissemination was occurred in only one patient (2.3%) with preoperative rupture of HCC. Intra hepatic tumor recurrence was occurred in 14 (47.2%) cases of 29 cases with R0 operation. Lung metastasis without intrahepatic recurrence was occurred in 2 cases with IVC tumor thrombus.

Conclusion: Complete mobilization of the liver from IVC was safe and feasible even in the case of huge HCC with severe compression of IVC. Intrahepatic recurrence may be most important prognostic factor especially in huge HCC.

P-11

Decreased Blood Loss Reduces Complications in Resection for Hepatocellular Carcinoma

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Background: The correlation between blood loss and the risk of postoperative complications was unclear in patients undergoing resection of hepatocellular carcinoma (HCC). To elucidate the relation between blood loss and complications in patients who undergo resection of HCC.

Methods: We studied 539 patients who had resection of HCC. Postoperative complications were recorded according to the modified Clavien-Dindo classification. Operative variables and liver functional markers were compared between patients

with grade III to V complications and those with no or grade I to II. Multivariate logistic analyses were performed to identify independent risk factors for complications. A spline regression analysis was used to estimate the probability of complications associated with risk factors.

Results: The rate of postoperative grade III to V was 28.6% (154/539), and the in-hospital mortality rate was 0.4% (2/539). Univariate analysis revealed that blood loss ($P = 0.0001$), tumor size ($P = 0.02$), operating time ($P = 0.0001$), and blood transfusion ($P = 0.0001$) differed significantly between patients with grade III to V and those with no or grade I to II. Multivariate analysis revealed that the factor most strongly related to complications was blood loss (odds ratio 1.68; 95% confidence interval [CI] 1.45–1.96, $P = 0.0001$). Spline regression analysis showed when blood loss exceeded 490 mL, the probability of complications exceeded 30% [31.1% [95% CI 18.6–47.1]]. When the probability of complications was 50% [95% CI 30.0–70.0], the blood loss was 820 mL.

Conclusion: Decrease in blood loss is accompanied by reduced risk of complications.

P-12

Sclerosed Hemangioma of the Liver: A Case Report

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We herein report a case of Sclerosed hemangioma of the liver which is an extremely rare type of benign hepatic tumor. The patient is a 59 year old man. 3 years ago, he noticed abdominal pain so that he received medical check-up then the tumor was detected on Ultrasonography (US) at a local hospital. On that time, he given a diagnosis of cavernous hemangioma of the Liver, and he was followed up annually on US. This year the size of tumor was increased in size up to 10 cm in diameter, so he was referred to our hospital.

The tumor, 10 × 9 cm in size was located in segment 7 and 8 of the liver. It revealed heterogeneous enhanced tumor on computed tomography (CT).

Magnetic resonance imaging (MRI) showed a low signal on T1-weighted and a high signal on T2-weighted images. This patient was negative for hepatitis B antigen and hepatitis C antibody. He underwent a right hepatectomy for possible malignant liver tumors, including intrahepatic cholangiocarcinoma or hepatocellular carcinoma. The following histological examination of the surgical specimen revealed the tumor to be a hepatic sclerosed hemangioma characteristic dense collagenous tissues. We report here on the case of this rare tumor.

P-13

**Mucinous Cystic Neoplasm of the Liver:
A Case Report**

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A 74-year-old female patient was noticed to have a cystic liver lesion, at a maximum 28 mm in diameter, in 2004. Since then, she had been followed up at a local hospital.

The lesion was initially bilocular, and gradually increased in size and developed into multilocular. The lesion has been considered as malignancy. Due to this situation, she was referred to our department in 2012.

CT showed a multilocular liver cyst, at a maximum 56 mm in diameter, with thickness and calcification of the septum, in segment 8. On MRI, both high and low intensity area was seen in the lesion on T1 weighted image, in contrast the lesion wholly indicated high intensity on T2 weighted image. CA19-9 was slightly elevated to 38 U/ml. ICG test was 8% and Child-Pugh classification was defined as A.

We performed laparotomy based on suspected diagnosis of mucinous cystic neoplasm (MCN) and patient's own request.

Intraoperatively, the tumor was observed protruding to the surface of the liver and adhered to the diaphragm. Therefore, we performed segmentectomy 8 with partial resection of the diaphragm, so as to avoid damage of the tumor. As for postoperative pathological finding, there was no atypia in the epithelium of the cyst, whereas ovalian-like stroma was observed in the stroma of the septum.

We present this case due to rare report of mucinous cystic neoplasm with ovalian like stroma of the liver.

P-14

**A Case of Reconstruction of the Diaphragm
after Surgery for Ruptured Hepatocellular
Carcinoma**

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Seventy-four years old woman complained dizziness. The patient was referred to our hospital because of anemia and cystic lesion in the right liver. CT and MRI examination revealed tumor 7 cm in diameter extended to the diaphragm. Preoperative diagnosis of this tumor was diaphragm origin.

Latissimus dorsi muscle flap was obtained for reconstruction of the diaphragm. Because tumor invaded to the

right lung, partial resection of the lower lobe was done. Liver parenchyma was ruptured and hematoma existed. Since hepatic tumor is detected by intra-operative ultrasonography and spontaneous rupture of the HCC was considered. Right hepatectomy was performed.

Diaphragm was reconstructed by latissimus dorsi muscle flap with horizontal mattress suture. The patient discharged on 17 postoperative day. However pleural effusion was prolonged on outpatient clinic, aspiration was not necessary.

Pathological finding was moderate differentiated hepatocellular carcinoma invaded to the diaphragm. The patient is alive more than 5-years after surgery.

In conclusion, latissimus dorsi muscle flap is considered as effective and anti-infectious procedure for reconstruction of the diaphragm.

P-15

**Effects of the Trans-Arterial
Chemoembolization on the Hepatic Artery
Complications in Liver Transplantation**

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Background: Hepatic artery complication (HAC) in patients underwent liver transplantation is an important factor for worse outcomes and graft loss. Transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC) is directly applied in HA and may injury it. Herein, we describe the relationship between the pre operative TACE and the apparition of HA (histological and clinical) complications.

Patients and Methods: All patients with HCC underwent liver transplantation in our center between January 2009 and October 2012 are included in this retrospective study and divided in 2 groups: TACE (group 1) and No TACE (group 2). HA complications are reviewed and compared. The recipient HA (close to the anastomotic site) underwent to histological analysis to detect histological wall injury.

Results: Sixty-six patients were reviewed, 32 for group 1 and 34 for group 2. Both groups were similar for gender, age, cirrhosis causes, and ASA score. There were more patients classified 2 in WHO performance scale, CHILD C, and less CHILD A in the group 1 with a p value of 0.0052, 0.0078 and

0.0002, respectively. Twelve patients were within Milan criteria in group 1 and 20 in group 2 ($p = 0.0345$). TACE were selective with drug-eluting beads in 18 patients. At a mean follow up of 9.5 months, 8 HAC occurred; 5 in group 1 and 3 in group 2 ($p = 0.2953$). In both groups there was one thrombosis. Furthermore, 4 and 2 non thrombotic complications were noticed in the group 1 and 2, respectively. Three of our 4 deaths were due to HAC, 2 occurred in group 1, and 1 in group 2. Histological screening showed 7 HA injuries in group 1 and 2 in group 2 ($p = 0.0501$).

Conclusion: Even if our study did not show any statistical difference between the two groups, we found a trend that deserves further studies with a largest cohort of transplanted patients.

P-16

East Meeting West: The Changing Perspectives in Management of Hepatocellular Carcinoma, a Single Centre Experience from North India

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Aims and Methods: We retrospectively reviewed the records of patients presenting to Sir Ganga Ram Hospital, New Delhi, India from Nov 2000 to Sep 2012, who were diagnosed as Hepatocellular carcinoma (HCC). Etiology, clinical presentation and treatment modalities used were evaluated and compared with the previous published studies from India.

Results: A total of 114 patients were included in the study. Their mean age was $59 (\pm 10)$ years and 88% were males. HBV was the etiological factor in 47 (41%) of patients (including 4 patients with co-infection with HCV). The etiology of HCC in rest of 67 (59%) patients was: HCV (21%), cryptogenic (20%), alcohol (16%), and miscellaneous (2%). The mean age of presentation was (59 ± 10) years. Clinical evidence of cirrhosis was present in 86% of patients. The median CTP score was 8 (range 5 to 13). Ascites was present in 58% of patients. In 47% of patients the tumor was single, mostly (77%) involving the right lobe, with median size of tumor 7 (range 0.7 to 16) cm. In rest of 53% of cases the tumors were more than 2 or multicentric. Associated portal vein thrombosis was present in 33% of cases. Their BCLC staging was as follows: A 20%, B 18%, C 34%, and D 28%. 6 patients were treated with liver transplantation (LDLT), 6 patients were treated with partial hepatic resection; 5 patients underwent 8 sessions of radiofrequency ablation (RFA); 10 patients underwent trans-arterial chemo-embolisation (TACE) and 4 underwent trans-arterial radioembolisation (TARE). 8 patients received sorafenib and remaining 75 patients were treated with supportive care.

Conclusion: Thus, HCC has not changed in India with respect to etiology, presenting features, portal vein thrombosis involved by the tumor; but management of HCC has definitely changed by virtue of various armaments in treatment modalities including LDLT, RFA, TARE, TACE, Sorafenib thereby improving the morbidity and mortality.

P-17

Cryoablation Increases the Chance of Local Control for Primary Hepatocellular Carcinoma than Radiofrequency Ablation and Microwave Coagulation Therapy

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Background: Although cryoablation (Cryo) has been advocated as an effective local treatment for hepatocellular carcinoma (HCC), data are lacking regarding its outcomes in comparison with radiofrequency ablation (RFA) and microwave coagulation therapy (MCT). The aim of this study was to clarify the benefits and disadvantages of each modality for primary HCC.

Methods: We reviewed outcomes of 120 patients with primary HCCs (< 5 cm) who underwent local treatment (Cryo: $n = 55$ and RFA/ MCT: $n = 65$) between 1998 and 2011. The primary endpoint was local recurrence free survival (LRFS). The secondary endpoints were complication rates and the length of hospital stay.

Results: Age, sex, Child-Pugh score, and background liver disease were identical between both groups. The Cryo group had larger tumors (mean $\pm$ standard error tumor size: Cryo 2.55 ± 0.75 cm vs. RFA/MCT 1.96 ± 0.72 cm, $P < 0.001$). The LRFS was higher in the Cryo group than in RFA/MCT group (2270.0 ± 240.8 days vs. 1940.7 ± 269.5 days: $P = 0.116$). The Cox proportional hazards multivariate analysis revealed that Cryo as the treatment of choice was an independent predictive indicator of improved LRFS (HR, 0.403 [95% CI: 0.202–0.807], $P = 0.010$). On the contrary, tumor size (for each 1 cm increase, HR, 1.635 [95% CI: 1.038–2.574], $P = 0.034$) and Child-Pugh score ≥ 6 (HR, 2.166 [95% CI: 1.179–3.979], $P = 0.013$) were negative prognostic factors for LRFS. Subgroup analysis showed that the LRFS for tumors ≤ 2 cm was similar between the 2 groups. However, if the tumor size was greater than 2 cm, the LRFS of the Cryo group was superior to RFA/MCT (2400.0 ± 287.4 days vs. 1177.9 ± 366.5 days: $P = 0.004$). The complication rates (Cryo 10.9% vs. RFA/MCT 10.8%: $P = 0.980$) and the length of hospital stay (9.45 ± 5.33 days vs. 9.52 ± 5.90 days: $P = 0.947$) were similar in both groups. No mortality was observed in the entire cohort.

Conclusion: Cryo provides significantly higher chance of local control for primary HCCs compared with RFA/MCT, particularly if the tumor size exceeds 2 cm. Risk of adverse events are at least equivalent to those of RFA/MCT even in patients with marginal to poor liver function. Cryo is a promising local ablative option in an era of rising incidence of HCC.

P-18

Hepatocellular Carcinoma with Extrahepatic Metastasis; Prognosis and Efficacy of Systemic Chemotherapy Including Sorafenib

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Backgrounds and Aims: Despite significant advances in the treatment of intrahepatic lesions, the prognosis for hepatocellular carcinoma (HCC) with extrahepatic metastasis remains poor. The aim of this study was to elucidate the prognosis of patients with this disease and to evaluate the efficacy of systemic chemotherapy.

Methods: In study I, a total of 342 patients with extrahepatic metastasis of HCC were enrolled. The metastasis was diagnosed upon the initial presentation of HCC in 28 cases and during the follow-up period in the remaining patients. We analyzed the clinical feature and the prognosis. In study II, we analyzed 48 HCC patients with extrahepatic metastasis who were treated with sorafenib from May 2009 to September 2011. We also analyzed 166 HCC patients with extrahepatic metastasis who were treated with systemic combination therapy with intravenous continuous 5-fluorouracil and pegylated interferon alfa-2a (sFI) in January 2004 and May 2009, when sorafenib was not licensed yet in Japan.

Results: [Study I] The most frequent site of extrahepatic metastasis was the lung, followed by the lymph node, bone, and adrenal gland. These metastases were directly related to death in 23 cases only (7.6%). The median survival time after diagnosis of extrahepatic metastasis was 8.1 months. Based on analysis of prognostic factors, we developed a scoring system to predict the prognosis that assessed uncontrollable intrahepatic lesions, extent of vascular invasion, and the performance status. [Study II] All the patients in sorafenib group were in Child-Pugh class A, whereas those in sFI group, consisted of 127 patients (76.5%) in class A and 39 (23.5%) in class B. The response rate was 10.4% in sorafenib group and 9.6% in sFI group. Disease-control rate was 41.7% in sorafenib group and 30.7% in sFI group. The median time-to-progression

was 3.1 months in sorafenib group and 2.0 months in sFI group (P=0.83). The median survival time (MST) was 10.8 months in sorafenib group and 5.4 months in sFI group (P=0.008). When we analyzed only Child-Pugh class A patients in the two groups, MST was 10.8 months in sorafenib group and 7.5 months in sFI group (P=0.04).

Conclusions: The controllability of intrahepatic lesions, presence of vascular invasion and performance status are important prognostic factors in cases of HCC with extrahepatic metastasis. Sorafenib is standard therapy for such patients in Child-Pugh class A. sFI is one of the treatment options for Child-Pugh class B patients and sorafenib failure.

P-19

Risk Factors for Early Death after Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma

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Background: The indication of transcatheter arterial chemoembolization (TACE) remains controversial in patients with unresectable hepatocellular carcinoma (HCC).

Methods: We studied 355 patients who underwent TACE for unresectable HCC to identify risk factors for early death (within 6 months after initial TACE).

Results: Among them the 51 patients (14%) died within 6 months after initial TACE. Multivariate analyses identified the following risk factors for early death: extensive vascular invasion (odds ratio 5.46; 95% confidence interval 1.91–15.6; P = 0.0015), tumor number ≥ 10 (5.24; 2.07–13.2; P = 0.0005), tumor size ≥ 10 cm (4.27; 1.78–10.6.9; P = 0.0018), serum alpha-fetoprotein level ≥ 1000 ng/ml (4.07; 1.93–8.55; P = 0.0002), and Child-Pugh class B or C (3.83; 1.60–9.17; P = 0.0025). We developed an algorithm in which each of factors was assigned a score of 1 point to predict the risk of early death. No patient had a score of 5 points, and only 4 patients had a score of 4 points. Patients who had undergone TACE could be significantly stratified into the 3 groups according to the point score and the corresponding 6-month survival rate and median survival periods were as follows: 0 points, 97% (95% confidence interval 95–99%) and 38 months (95% confidence interval 35–41 month); 1 point, 85% (78–92%) and 22 months (13–30 month); and 2 to 4 points, 49% (36–62%) and 5 months (3–8 month), respectively (P<0.0001).

Conclusion: In patients with HCC may not be good candidates for TACE.

P-20

The Short-Term Outcome of Postoperative ¹³¹I-labeled Metuximab Adjuvant Therapy for High Recurrence Risk Hepatocellular Carcinoma

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Background: Hepatocellular carcinoma(HCC) is the most common cancer in primary liver cancer. Macroscopic vascular invasion is known to be related with postoperative high recurrence rate. ¹³¹I-labeled Metuximab (Licartin) which is generated by ¹³¹I-labelling of the murine monoclonal antibody fragment HAb18 F(ab')₂ derived from HAb18G/CD147 can give safe and effective therapy to hepatocellular carcinoma in previous researches. The aim of this study was to find out whether ¹³¹I-labeled Metuximab can reduce the early recurrence rate for the patients with macroscopic vascular invasion after hepatectomy.

Methods: Between April 2009 and April 2012, there were 125 HCC patients who underwent operation by one doctor at Department of Hepatobiliary Surgery, Tianjin Medical University Cancer Hospital. To the patients with macroscopic vascular invasion or other high risk recurrence factors, we gave them ¹³¹I-labeled Metuximab as adjuvant therapy prospectively, other patients with the same factors without ¹³¹I-labeled Metuximab as control group. All the patients were followed up each 3 months. Clinical data were collected and analyzed.

Result: Among these 125 HCC cases, 13 (10.4%) had macroscopic vascular. 9 in the Control Group (did not received any adjuvant treatment). 4 cases with macroscopic vascular, 1 case with bile duct invasion, 1 case with microvascular invasion, low differentiation and satellite in the Licartin group. The median disease-free survival were 9 month and 4 month(P = 0.006) in the Licartin Group and Control Group respectively. The same trend also be found in the overall survival, the estimate mean value were 20.167 ± 3.467 and 7.444 ± 0.876 (P = 0.046) in the two groups respectively. There were no significant difference in recurrence rate between two groups.

Conclusions: To the HCC patient with macroscopic vascular invasion, resection is the first choice, and Licartin may be a kind of potential effective adjuvant treatment to improve the prognosis. More cases and randomized controlled trial are needed to confirm it.

P-21

Focal Fatty Liver during Chemotherapy Period for Lung Cancer: A Case Report

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We reported that a case of focal fatty liver for the duration of chemotherapy for lung cancer. It was hard to make a differential diagnosis from hepatocellular carcinoma.

The patient is a 64 year-old man. He underwent left upper lobectomy of the lung for lung cancer about 3 years ago. And he also underwent partial nephrectomy for renal cell carcinoma. After that, he underwent γ-knife therapy for brain metastasis from lung cancer.

After γ-knife therapy, chemotherapy was performed for 4 times (carboplatin+ pemetrexed sodium hydrate).

The tumor was detected on Computed Tomography at the medical checkup.

CT showed a tumor 2 cm in diameter in Segment 7, this tumor was not enhanced in both the arterial phase and the portal phase. MRI showed this tumor was high intensity in the T1WI and iso intensity in the T2WI. The uptake of EOB was reduced.

Biopsy yielded a highly suspicious of diagnosis of hepatocellular carcinoma.

Based on the diagnosis of hepatocellular carcinoma, we performed laparoscopic assisted partial resection of segment 7 of the liver.

Macroscopic specimen revealed accumulation of small yellowish spots in Segment 7. Rest of the liver looks NASH. Microscopic specimen yielded a diagnosis of focal fatty change of the liver and NASH.

According to these findings, this tumor was given a diagnosis of focal fatty liver.

P-22

Liver Micro-Environment and HCC Growth

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Background: Thrombocytopenia has been reported to be a surrogate for cirrhosis, but the HCC phenotypes associated with and without cirrhosis are not well studied.

Aims: To compare characteristics of HCC patients with and without associated thrombocytosis.

Methods: Records were examined of a cohort of 668 biopsy-proven and randomly presenting unresectable HCC patients, who were dichotomized for presence (platelets <125 x

$10^9/L$) or absence (platelets $125\text{--}400 \times 10^9/L$) of thrombocytopenia.

Results: Patients with normal platelets had larger tumors, more tumor nodules and longer survival than in the thrombocytopenia group. They also had more normal total plasma bilirubin, albumin and prothrombin times, yet had higher GGTP, ALKP and AFP levels.

Conclusions: Thrombocytopenia in association with HCC occurs in patients with smaller tumor sizes, worse liver function and poorer survival, supporting the importance of host factors and liver micro-environment in HCC patients.

P-23

Sparing of Hepatic Vein in Contact with Colorectal Liver Metastases at the Caval Confluence based on Preoperative and Intraoperative Imaging Criteria: An Intention to Treat Approach

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Introduction: Major hepatectomies are generally selected for tumors in contact or involving the hepatic vein (HV) at its caval confluence (CC). Whenever a conservative surgical approach is attempted, HV reconstruction is anyway recommended. The use of criterion based on intraoperative ultrasonography (IOUS) may drastically limit the need for more extensive hepatectomy in these conditions. An intention-to-treat prospective study to validate this hypothesis has been conducted in a cohort of patients carrier of at least one colorectal liver metastasis (CLM) in contact with a HV at CC.

Methods: Thirty-eight patients showing at preoperative imaging at least one CLM in contact with a HV at CC were enrolled. Based on IOUS findings, 3 patterns of presentation were recognized and respective surgical policies were established: type A – HV in contact with CLM for less than 1/3 of its circumference, regardless of longitudinal extension: vein sparing by means of progressive detachment of the lesion was planned; type B: HV involvement by CLM ranging from 1/3 to 2/3 of its circumference, regardless of longitudinal extension: vein sparing with possible HV wall resection and reconstruction by direct suture or patching was planned; type C: HV involvement for $\geq 2/3$ of its circumference by CLM with or without interruption of vessel wall at IOUS: vein resection was planned.

Results: In 28 (74%) patients a J-shaped thoracophrenolaparotomy was performed. At IOUS, 17 (45%) patients confirmed a Type A contact, 12 (32%) a Type B, while 9 (23%) a Type C. No major or extended hepatectomy was

required. Complete detachment of the tumor from HV was feasible in 29 (77%) patients, HV reconstruction with direct suture in 13 patients (34%), while HV resection was carried out in 9 (23%) patients. Median operation and clamping time was 501 min (range 303–889) and 121 min (range 56–279), respectively. Preconditioning was never adopted. Total vascular exclusion with caval flow preservation was used in 1 patient. Blood transfusions rate was 16% (6/38). Postoperative mortality was nil. Overall and major morbidity rate was 39% (15/38) and 5% (2/38), respectively. No local recurrences have been observed at a median follow-up of 13 months (range 6–34).

Conclusions: Preserving remnant liver parenchyma in hepatectomy is the key factor to ensure better results in terms of postoperative mortality and morbidity. The proposed tumor-vessel classification based on IOUS-criteria, has been validated on an intention to treat perspective and in all but one patients was able to predict the proper surgical strategy. Adopting these criteria major hepatectomies can be avoided in favor of a surgical policy which is safe, featured by acceptable oncological radicality, and able to expand indications for surgery.

P-24

Signal Intensity Patterns and Natural Histories of Borderline Lesions of HCC on Hepatobiliary Phase Gd-EOB-DTPA (EOB) Enhanced MRI

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Purpose: To elucidate the incidence of signal intensity patterns of borderline lesions of HCC on hepatobiliary phase Gd-EOB-DTPA (EOB) enhanced MRI and clarify the natural histories of these lesions.

Materials and Methods: Total 99 borderline lesions of HCC were identified by angiography-assisted CT in 63 patients. EOB-enhanced MRI was performed within 1 month before or after angiography-assisted CT, and the signal intensity of borderline lesions on hepatobiliary phase were analyzed. Progress rate from borderline lesions to hypervascular HCC were calculated with the Kaplan-Meier method among each signal intensity groups of nodules seen on hepatobiliary phase of EOB-enhanced MRI. Log-rank method was applied for comparison of progress rate from borderline lesions to HCC. A two-sided P value of less than 0.05 was considered statistically significant.

Results: On HBP-EOB-MRI, 41.4% of the borderline lesions showed hypo-, 42.4% showed iso-, and 16.2% showed hyperintense, compared to background liver paren-

chyma. Within them, 78 were followed using multiphasic contrast-enhanced CT and/or MRI (follow up period range, 14 to 1240 days). Overall progress rate from borderline lesions to hypervascular HCC were 10% in 1 year, 14% in 2 year and 20% in 3 year follow up period. Eight of 32 hypointense borderline lesions and 2 of 35 isointense borderline lesions progressed to hypervascular HCC over a follow-up period of 134 to 985 days. Progress rates to HCC in hypointense borderline lesions were 17% in 1 year, 28% in 2 year and 41% in 3 year follow up period, and in isointense borderline lesions were 7% in 1 year, 7% in 2 year and 7% in 3 year follow up period. No hyperintense borderline lesions progressed to HCC in follow up period. There are significant differences in progress rate from borderline lesions to HCC in both between 'isointense and hypointense' and 'hyperintense and hypointense' borderline lesions ($P = .032$ and $P = 0.037$, respectively).

Conclusion: Although borderline lesions of HCC may show hypo-, iso- and hyperintensity on hepatobiliary phase of EOB-enhanced MRI, hypointense borderline lesions are high risk to progress overt HCC.

P-25

The Gross Classification of Hepatocellular Carcinoma: Usefulness of Contrast-Enhanced US using Perfluorocarbon Microbubbles (Sonazoid)

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Purpose: This study investigated the usefulness of post-vascular images on contrast-enhanced ultrasonography (CE-US) in the gross classification of hepatocellular carcinoma (HCC) in comparison with contrast-enhanced CT (CE-CT) findings.

Methods: This is a prospective study with consecutive HCC patients who had both CE-US and CE-CT prior to surgical resection. Fifty-one patients (32 men, 19 women; mean age, 68.9 years) with 61 hepatic malignancies were enrolled. The maximal diameters of all tumors ranged from 1.0 to 5.0 cm (mean $\pm$ SD, 2.5 cm $\pm$ 1.1). Weighted kappa statistic were used to assess the agreement of the US or CT findings versus the results of macroscopic configurations.

Results: Thirty-nine tumors were macroscopically diagnosed as simple nodule type, 19 tumors as simple nodular type with extranodular growth, and 3 tumors as confluent multinodular type from the resected specimen. The diagnostic accuracy was 86.9% (53/61) for CE-US and 65.6% (40/61) for CE-CT ($p = 0.036$, Chi square test). Correlation analysis between gross classification using CEUS and macroscopic final results gave a kappa value of 0.74, which was considered a good correlation. On the other hand, kappa coefficient

showed difference in a value of 0.38 between gross classification using CE-CT and macroscopic final results.

Conclusion: CE-US is a more reliable tool to evaluate the gross type of HCC than CE-CT. Accurate gross classification using imaging is considered to be essential for the determination of the correct treatment strategy and the estimates of the patients' prognosis.

P-26

A Novel Navigation System for Liver Resection

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Innovation

Three-dimensional simulation of liver resection has been proved to be useful for surgical planning, and the next step should be a development of intraoperative guidance which navigates resecting plane according to the preoperative plan. In this study, we devised a novel surgical navigation system for liver resection.

The system consists of an intraoperative ultrasonography (IOUS), an electromagnetic tracking device, and a workstation. By the system, a small electromagnetic sensor is attached to the IOUS probe so as to track the probe position. Adjacent to ultrasound image, corresponding multiplanar reconstruction images of preoperative computed tomography (CT) and/or magnetic resonance (MR) are simultaneously reconstructed and displayed on a television monitor. In this way, surgeons can identify hepatic tumor(s) by comparing images of IOUS with those of preoperative CT/MR.

In addition, preoperative simulation images, in which the liver parenchyma to be resected is highlighted by color, can be overlaid on the CT images. During hepatic parenchymal transection or the intervals for intermittent Pringle maneuver, the resection plane observed by IOUS can be compared with that on the preoperative simulation images. The reference image in the preoperative simulation shows the resection line between the liver parenchyma to be resected and the liver remnant, while the IOUS shows the actual resection plane, which is visualized as a hyper-echoic plane. By comparing the reference image and the IOUS image, it can be easily evaluated whether the resecting plane coincides with the preoperative surgical plan.

The navigation system was demonstrated to be feasible in 16 cases of liver resections, and is expected to contribute to safe and accurate liver surgery.

P-27

Hemodynamic Study of Hepatic Nodules using Contrast-Enhanced Ultrasonography (CEUS) with Sonazoid

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Background and Aim: Though only 1–2 nodules can be examined per session, contrast-enhanced ultrasonography (CEUS) provides more detailed hemodynamic information than CT or MRI and has no adverse effects. We examined nodules using CEUS to clarify its diagnostic utility, focusing especially on arterial and early portal phase hemodynamics of hepatocellular carcinoma (HCC).

Methods: Starting in 2007, we examined 1427 patients with hepatic nodules using CEUS with Sonazoid®. In 130 cases with 135 hepatocellular nodules, CEUS findings were compared with pathological features. There were 110 HCCs (6 poorly-, 69 moderately- and 35 well-differentiated), 5 large regenerative nodules and 20 hyperplastic nodules. We focused on the feeding artery and tumor enhancement during the arterial and early portal phases. The wash-out time, followed by tumor enhancement, was determined. Sonazoid, 0.01 ml/kg, was administered intravenously. Observations were made starting immediately after injection for 45 sec, and thereafter at 1, 2, 3, 5, 10, 20, and 30 min (10–20 sec each). The main imaging devices used were Prosound α 10, F75 and Ascendus (Hitachi-ALOKA, Japan).

Results: The contrast medium reached the intrahepatic artery at 17 sec (median). The initial portal flow was observed at 23 sec. All poorly-differentiated HCC showed partial hyper-enhancement in the arterial phase. Early wash-out was evident from 38 sec to 3 min. All moderately-differentiated HCC showed arterial hyper-enhancement but wash-out was slightly delayed, occurring between 1 and 10 min. Well-differentiated HCC showed various patterns of arterial enhancement (6 hyper, 6 iso and 23 hypo) and wash-out. Only 5 nodules showed wash-out indicating malignancy, though wash-out was delayed (5–30 min). Of the 23 nodules hypo-enhanced in the arterial phase, 30% remained hypo at all time points throughout the examination, suggesting a minimal arterial and portal supply. The remaining 70% showed iso-enhancement in the early portal phase suggesting portal supply. Iso-enhancement throughout the observation period was seen in 4 well-differentiated HCC, hemodynamics the same as those of a large

regenerative nodule. Another 4 showed arterial hyper-enhancement and no wash-out, mimicking benign hyperplastic nodules. Most of the benign hyperplastic nodules showed arterial enhancement, but wash-out was seen in 15% including 2 focal nodular hyperplasia and 1 alcoholic nodule.

Conclusion: Detailed knowledge of hemodynamic characteristics on CEUS with Sonazoid facilitates distinguishing among hepatic nodules and, possibly, selecting the optimal treatment.

P-28

Is a Fluorescence Navigation System with Indocyanine Green Effective Enough to Detect Liver Malignancies?

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Background: In liver surgery, in order to achieve absolute removal of tumors, it is essential to recognize even small tumors and to ensure the accurate surgical margin intraoperatively. Several reports have shown the efficacy of a fluorescence navigation system (FNS) with indocyanine green (ICG) to detect liver malignancies during hepatectomy. However, the real accuracy of this procedure is not yet clear. The aim of this study was to analyze the actual efficacy of ICG-FNS in cirrhotic and non-cirrhotic livers.

Methods: Ten cirrhotic whole livers were obtained from living donor liver transplant (LDLT) recipients. The original diseases included hepatitis C virus (HCV)-cirrhosis in 8, hepatitis B virus (HBV)-cirrhosis in 1, and alcoholic cirrhosis in 1. In addition, we evaluated twenty-three noncirrhotic liver specimens obtained from patients who underwent hepatectomy for various kind of liver tumors [hepatocellular carcinoma (HCC) in 12, metastasis of colorectal cancer in 9, cholangiocarcinoma in 1, and hepatic carcinoid in 1]. As a fluorescence source, we used ICG (Diagnogreen, Daiichi Sankyo, Tokyo, Japan), which had been intravenously injected before surgery at a dose of 0.5 mg per of body weight as part of a routine liver function test. The intervals between the ICG injection and surgery ranged from 1 to 3 days (median, 2 days). As a fluorescent imaging tool, we used Photo Dynamic Eye-II (PDE-II, Hamamatsu Photonics, Hamamatsu, Japan). All surgical specimens were analyzed macroscopically and pathologically.

Results: In the patients with a cirrhotic liver, most nodules illuminated by ICG-FNS were diagnosed as regenerative nodules pathologically. The positive predictive value was 5.4%. There was a significant difference in positive

predictive value to detect malignant liver tumors between cirrhotic liver and non-cirrhotic liver (5.4% vs 100%, $p < 0.0001$). There were significant differences between the numbers of preoperatively detected tumors and the number of both illuminated nodules and those macroscopically recognized as tumors ($p < 0.001$). Moreover, there were also significant differences between the numbers of nodules pathologically diagnosed as tumors and the number of both illuminated nodules and nodules macroscopically recognized as tumors ($p < 0.001$). In the non-cirrhotic livers, eleven of thirty-three (32.4%) tumors were not recognized by ICG-FNS through the liver surface before resection. There was a significant difference in the depth from the liver surface to tumor between illuminated nodules and non-illuminated nodules (1.5 mm vs 11.6 mm, $p < 0.01$). Although there was no significant difference, non-illuminated nodules tended to be smaller than illuminated nodules (illuminated nodules, 32.4 mm vs non-illuminated nodules, 20.7 mm; $p = 0.058$).

Conclusions: The efficacy of ICG-FNS was not sufficient to detect liver malignancies in both cirrhotic and non-cirrhotic livers.

P-29

A New Method for Assessment of Liver Functional Reserve using a 99mTc GSA Liver Scintigraphy

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Background: Preoperative estimation of the liver functional reserve is important in liver surgery. Technetium-99m diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (Tc-GSA) scintigraphy has been used for this aim. Although the LHL15 and HH15, calculated from the counted rate during Tc-GSA scintigraphy, have been widely used as indices for evaluating liver functional reserve, these indices have several problems. 'Index of convexity' is another index which has been newly advocated by Miki et al. We evaluated this new method using the data extracted from the patients who underwent liver resection in our institute.

Methods: One hundred eighty-four consecutive patients who underwent Tc-GSA scintigraphy and ICG clearance test were included in this study. We determined the correlation coefficient between the Index of Convexity and ICG-R15, retrospectively. Index of Convexity is calculated as $(L(15) \times 2 - L(3) - L(27)) / (L(27) - L(3))$, where $L(t)$ means the radiation counts at t minutes after Tc-GSA injection.

Results: Correlation coefficient between ICG retention rate at 15 minutes (ICG-R15) and index of convexity was

-0.6179 . Linear regression equation is $ICG-R15 = 56 - 75 \times \text{Index of Convexity}$.

Conclusion: The Index of Convexity is a very simple and reliable index for assessing liver functional reserve.

P-30

Indication and Efficacy of Portal Vein Embolization for the Patients Undergoing Major Hepatectomy

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Objectives: To evaluate the influence of preoperative portal vein embolization (PVE) on short-term outcomes after major hepatectomy.

Methods: The effects of embolization and hepatic resection rate were reviewed in 256 patients who underwent PVE between January 2001 and August 2012. Postoperative morbidity was compared with 128 patients who underwent (extended) right hepatectomy or trisectionectomy without PVE.

Results: Median age of the 256 patients was 65 years old (range, 33–88) and 171 patients (67%) were male. Types of tumor was hilar cholangiocarcinoma, 76; gallbladder cancer (GBCA), 44; intrahepatic cholangiocarcinoma, 42; hepatocellular carcinoma (HCC), 41; metastatic liver cancer, 44, and others, 9 patients. Median ratio of future remnant liver (FRL)/total liver volume was 35% (range, 21–59) before PVE and increased to 48% (range, 28–79) after median interval of 17 days. PVE related complications occurred in 7 patients including hemobilia, migration of embolization material, portal vein thrombosis, liver abscess, pseudoaneurysm, and toxicoderma. Hepatectomy as scheduled was performed in 225 patients (88%). Resection was abandoned due to tumor progression in 19, poor physical condition in 2, and insufficient hypertrophy of FRL in another patient. Tumor was resected by minor hepatectomy or other type of procedure due to insufficient hypertrophy of FRL in 6 and overestimation of the tumor extension in 3 patients. Insufficient hypertrophy of FRL was frequent in HCC patients (vs. non-HCC; 10% vs. 1%; $P = 0.01$), while tumor progression that resulted in exploratory laparotomy occurred often in GBGA patients (vs. non-GBGA; 20% vs. 5%; $P < 0.01$). To compare the 225 patients with 128 patients without PVE, preoperative ICG-R15 was comparable (7.7% [0.3–63.2] vs. 7.0% [0.1–26.4]; $P = 0.11$), but more patients with PVE had biliary tract cancer (63% vs. 26%; $P < 0.01$) and combined resection of other organs including extrahepatic bile duct or portal vein were more frequently performed (67% vs. 40%;

$P < 0.01$). The incidence of postoperative morbidity was higher in patients with PVE (52% vs. 35%; $P < 0.01$). However, the incidence of hepatic insufficiency defined as postoperative maximal serum total bilirubin value > 7 mg/dl (10 patients vs. 4 patients; $P = 0.78$) and mortality (2 patients vs. 1 patient; $P = 1.00$) were comparable. Multivariate analysis in the 353 patient who underwent scheduled hepatectomy revealed intraoperative red blood cell transfusion ($HR = 6.68$; 95% CI, 1.44–30.99) as only independent predictor of postoperative hepatic insufficiency.

Conclusion: PVE was indicated frequently for the patients with biliary tract cancer that requires complicated surgical procedures such as extrahepatic bile duct resection and postoperative morbidity rate was higher compared with major hepatectomy without PVE. However, the risk of hepatic insufficiency or mortality was minimal. This study suggested PVE contributed to improving the safety of major hepatic resection.

P-31

The Dysfunctional Area and Congestive Area after Hepatectomy with Main Hepatic Vein Resection

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Background: To evaluate the liver function in the congestive area of the remnant liver after major hepatectomy with middle hepatic vein (MHV) resection.

Methods: From November 2009 through December 2011, 15 patients underwent hepatectomy including the MHV. Left hepatectomy (LH) including the MHV was performed in 11 patients and right hepatectomy (RH) including the MHV in 4 patients. Post-hepatectomy, the volume of the congestive area and dysfunctional area in the remnant liver was evaluated in all patients by gadoteric acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) within 1 month after surgery. The congestive area appeared as a hyperintense area on T2-weighted images. The dysfunctional area appeared as a low intensity area on hepatobiliary phase images. The proportion of the volume of the congestive area and the dysfunctional area to that of the entire remnant liver was defined as the congestive rate and dysfunctional rate, respectively.

Results: Thirteen of 15 patients showed a congestive area, and 14 of 15 patients showed a dysfunctional area in the remnant liver. The dysfunctional rate ($15 \pm 10\%$) was significantly larger than the congestive rate ($9 \pm 7\%$, $p = 0.0009$). The dysfunctional rate was associated with tumor invasion to the root of the MHV, and it was significantly larger in patients without tumor invasion to the root of the MHV ($19 \pm 9\%$) than in patients with ($6 \pm 5\%$, $p = 0.0186$).

Conclusion: Hepatectomy with MHV resection should be performed considering the dysfunctional area in the remnant liver, which is associated with tumor invasion to the root of the MHV.

P-32

Intraoperative Portal Venous Pressure is Associated with Long-Term Outcome after Curative Resection for Hepatocellular Carcinoma

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Background: The outcome of liver resection for hepatocellular carcinoma (HCC) has improved because of established techniques and better patient selection. Even in patients with portal hypertension, the preoperative definition of portal hypertension is still subjective. The aim of this study was to elucidate the influence of intraoperative directly measured portal venous pressure (PVP) on the outcome of liver resection in patients with HCC.

Methods: Between 1997 and 2009, a total of 177 patients underwent the direct measurement of PVP immediately after laparotomy. These patients were divided into two groups according to the PVP; $PVP \geq 20$ cm H₂O (high PVP group, $n = 48$) or $PVP < 20$ cm H₂O (low PVP group, $n = 129$). The influences of PVP on the survival rate, recurrence free survival rate and prognostic factors were analyzed.

Results: The 5-year survival rate was significantly higher in patients with a low PVP than a high PVP (63.7% vs. 31.4%, $P < 0.001$). The 5-year recurrence free survival rate was also significantly higher in patients with a low PVP than a high PVP (52.5% vs. 12.1%, $P < 0.001$). In a multivariate analysis, a tumor number ≥ 2 , tumor diameter ≥ 5 cm, high PVP, liver damage of class B, hepatic activity index (HAI) grading ≥ 7 and AFP ≥ 100 ng/ml were significant predictors of poorer survival after liver resection. A tumor number ≥ 2 , tumor diameter ≥ 5 cm and an HAI grading ≥ 7 were significant predictors of a poorer recurrence free survival based on a multivariate analysis.

Conclusion: The portal venous pressure was associated with the long term outcome of HCC after liver resection.

P-33

Relationship Between ICGR-15, and 99m Tc-GSA Liver Scintigraphy and Hematological Parameters

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Background: Indocyanin green retention at 15 min (ICGR-15) is commonly recognized as a reliable tool for the assessment of hepatic functional reserve. Technetium-99m galactosyl human serum albumin (99m Tc-GSA) SPECT scintigraphy is also clinically useful modality for the assessment of the residual hepatic function in liver surgery. The aim of this study was to determine the relationship between ICGR-15, and 99m Tc-GSA SPECT scintigraphy and the hematological parameters.

Methods: We reviewed 76 patients who underwent ICGR-15 and 99m Tc-GSA SPECT scintigraphy between May 2010 and October 2012 at our department of Yamagata university hospital. Correlation between ICGR-15, and the total liver uptake of 99m Tc-GSA, red and white blood cell count, platelet count, prothrombin activity, serum hemoglobin, hematocrit, albumin, total bilirubin, cholinesterase (ChE), cholesterol, aspartate amino transferase (AST) and alanine amino transferase (ALT) levels were assessed.

Results: There were no significant correlation between ICGR-15, and red and white blood cell count, platelet count, serum hemoglobin, hematocrit, cholesterol, and ALT levels. A strong correlation was observed between ICGR-15 and the total liver uptake of 99m Tc-GSA ($r = -0.759$, $p < 0.001$). Positive correlations were observed between ICGR-15, and AST ($r = 0.513$, $p < 0.001$) and serum total bilirubin levels ($r = 0.415$, $p < 0.001$). Negative correlations were observed between ICGR-15, and ChE ($r = -0.480$, $p < 0.001$), prothrombin activity ($r = -0.406$, $p < 0.001$) and serum albumin levels ($r = -0.393$, $p < 0.001$).

Conclusion: 99m Tc-GSA SPECT scintigraphy is also a useful modality for the assessment of liver function. As with serum cholinesterase, total bilirubin, albumin levels and prothrombin activity, AST may be a predictor of hepatic functional reserve.

P-34

CT Volumetry and GSA SPECT Scintigraphy Before and After Portal Embolization

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Prof. Makuuchi firstly reported clinical implication of preoperative portal embolization for reduce size of right lobe, and enlargement of the left lobe. We studied 59 case of right portal embolization. Mean 99mTc-GSA scintigraphy uptake of normal liver is about 65%.

The CT volume of the left lobe significantly increased from 431 square cm to 505 square cm. GSA uptake of the left lobe significantly increase from 23% to 35%. Jaundice group was defined as serum bilirubin level beyond 3 mg/dl at the time of portal embolization.

Increase ratio for jaundice group was significantly lower than without jaundice group.

Increase ratio of the left lobe undergoing biliary drainage in the embolized lobe ($n = 27$) and the unembolized (left) lobe only ($n = 11$) were evaluated. The net morphological hypertrophy ratio was significantly higher in livers that had undergone left lobe drainage only ($9.1 \pm 0.9\%$) compared with those in which there was drainage of the embolized lobes ($5.7 \pm 0.9\%$; $P = 0.03$).

Recently, postoperative liver failure was not occurred in our department, 99mTc-GSA uptake of the left lobe in the second week after PE was significantly smaller in patients who experienced postoperative liver failure (22%) than in patients without liver failure (37%). ($p < 0.01$)

In conclusion, in the non-embolized lobe, the functional increase in 99mTc-GSA uptake is more pronounced than suggested by the degree of morphological hypertrophy. Morphological hypertrophy is small for jaundice cases. Whenever possible, biliary drainage should not be performed in the lobe undergoing hepatectomy. 99mTc-GSA SPECT scintigraphy is useful for the evaluation of postoperative liver failure.

P-35

A New Prognostic Classification Scheme with Treatment Guidelines for Asian Hepatocellular Carcinoma (HCC) Patients: the Hong Kong Combined Liver Cancer (HKCLC) Classification

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Background: HCC patients in Asia mostly have different etiologies and have different treatment algorithm when compared with their Western counterparts. Despite the wide use in Western countries, the Barcelona Clinic Liver Cancer (BCLC) staging may not fit in the management of Asian patients. We aim to develop a new prognostic classification scheme with treatment guidelines for Asian HCC patients.

Methods: HCC patients treated at the Department of Surgery, Queen Mary Hospital between 1995 and 2008 were included. The scheme was developed by both statistical methodology and clinical judgment. Four established prognostic factors, namely ECOG PS, Child-Pugh grade, tumor status and presence of extrahepatic venous invasion/metastasis, were selected in building the scheme. A scoring system which assigns 'points' to each category of these 4 factors was developed using Cox regression on overall survival. The points and combined scores were referred to stratify patients to different staging with specific treatment recommendations.

Results: 3617 patients were identified. The scheme stratifies patients to stages I to V with distinct overall survival outcomes. Selected patients had benefited from more aggressive treatments than what were recommended in BCLC. In patients who were classified as stage B in BCLC but I/II in HKCLC, the survival benefit of radical curative therapies over TACE was substantial (5-year survival probability: 0.479 vs 0.175; $P < .0001$ by log-rank test). Similarly, in patients who were classified as stage C in BCLC but I/II in HKCLC, the survival benefit of radical curative therapies over systemic therapy was even more pronounced (5-year survival probability: 0.484 vs 0; $P < .0001$ by log-rank test). Furthermore, in patients who were classified as stage C in BCLC but III in HKCLC, the survival benefit of TACE over systemic therapy was also significant (3-year survival probability: 0.087 vs 0.011; $P < .0001$ by log-rank test).

Conclusions: The HKCLC scheme may be able to identify patients suitable for treatments more aggressive than BCLC's recommendations and thus yield a better survival outcome.

P-36

Validation of Kyoto Criteria as Expanded Selection Criteria for Liver Transplantation for Hepatocellular Carcinoma

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Background: We previously proposed expanded selection criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC), the Kyoto criteria, involving a combination of tumor number ≤ 10 , maximal diameter of each tumor ≤ 5 cm, and serum des-gamma-carboxy prothrombin levels ≤ 400 mAU/mL, and we have used these criteria since January 2007. In the present study, the usefulness of the criteria was prospectively and retrospectively validated.

Methods: One hundred and ninety seven patients with HCC who underwent living donor LT (LDLT) at our institute between February 1999 and October 2011 were enrolled in this study. Overall survival and the recurrence rate were investigated in patients classified according to the Kyoto criteria, the Milan criteria, or previous treatments for HCC. Tumor biological aggressiveness, including microvascular invasion and histological differentiation, according to selection criteria was also examined.

Results: The 5-year overall survival and recurrence rates in 57 patients who underwent LDLT both after implementation of the Kyoto criteria and within the Kyoto criteria were 80.2% and 7.2%, respectively. The 5-year overall survival rate for patients within the Kyoto criteria ($n = 146$, 82.5%) was significantly higher than that for the 49 patients exceeding them ($n = 49$, 42.2%) ($P < 0.001$). The 5-year recurrence rate for patients within the Kyoto criteria (4.4%) was significantly lower than that for patients exceeding them (50.9%) ($P < 0.001$). Tumor biology was significantly less aggressive in patients within the Kyoto criteria.

Conclusions: The Kyoto criteria are useful expanded criteria for LDLT for HCC and could help achieve favorable outcomes.

P-37

What is the Appropriate Treatment for HCC Within Milan Criteria in Japan?

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Background: The shortage of deceased donor has been still the critical issue in Japan. Around 90% liver transplantations are carried out using living donor. Although the indication of liver transplantation for patients with hepatocellular carcinoma (HCC) has been expanded in each institute, the public insurance guarantees exclusively patients with HCC within Milan criteria. The decision making of treatment method among hepatectomy (Hx), liver transplantation (LTx), radiofrequency ablation therapy (RFA) or transcatheter arterial chemoembolization (TACE) for patients with HCC is depend on many factors such as the liver function, the size of HCC and the number of HCC according to the Clinical Practice Guidelines for Hepatocellular Carcinoma 2009 in Japan.

Aim: The aim of this study is to evaluate the outcome of each therapy retrospectively and to propose appropriate therapy for patients with HCC within the maximal size ≤ 3 cm and the number ≤ 3 .

Patients: Two hundred and twenty two patients who were referred to our hospital first time and underwent some treatment for HCC within the maximal size ≤ 3 cm and the number ≤ 3 from January 2006 to December 2011 were enrolled.

Results: The patients of LTx group were statistically younger than other groups ($P < 0.0001$). Child-Pugh classification of LTx group was statistically advanced than those of other groups ($P < 0.0001$). The disease free survival (DFS) of LTx group was statistically longer than those of other groups. The overall survival (OS) of each group was not statistically different. In Hx group, a subgroup with advanced HCC, 2–3 nodules and 2–3 cm in maximal size, showed statistically short DFS and OS than another subgroup with less advanced HCC ($P = 0.002$, $P = 0.03$). In the subgroup of patients younger than 60 years old, the OS of LTx group was statistically longer than that of Hx group ($P = 0.04$).

Conclusions: Among the patients with early HCC within the maximal size ≤ 3 cm and the number ≤ 3 , patients younger than 60 years old who had HCC, 2–3 nodules and 2–3 cm in maximal size, should be recommended to receive liver transplantation, taking donor availability into consideration.

P-38

Comparison of the Characteristics of Hepatocellular Carcinoma between Non-B Non-C type and B or C Type

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Background: Recently, the proportion of hepatocellular carcinoma (HCC) patients without viral infection is increasing.

Methods: Retrospectively collected clinicopathologic data was compared for HCC patients with and without hepatitis B virus (HBV) and/or hepatitis C virus (HCV). Between 1994 and 2007, a total of 257 patients with HCC underwent curative resection at our department. There were 73 patients without viral infection (nBnC group). Of the remaining 184 patients (B/C hepatitis group), 47 were with HBV, 140 with HCV and 3 with HBV and HCV.

Results: Patients in the nBnC group were older (nBnC versus B/C: 70 versus 67 years old) and had lower level of indocyanine green retention rate at 15 minutes (ICGR15) (13.9 versus 16.1 percent). α -fetoprotein (AFP) level were higher in the nBnC group (11.8 versus 33.9 ng. per ml). Major hepatectomy (more than 3 segments) was performed more frequently in the nBnC group (39 versus 18 percent). Maximum diameter of the resected tumor was larger in the nBnC group (4.5 versus 3.7 cm). The background liver cirrhosis was more frequent in the nBnC group (26 versus 51 percent). Recurrence free survival and overall survival were equivalent in the both groups. Multivariate analysis revealed that background liver cirrhosis and blood loss over 1000 ml were negative prognostic factors for overall survival.

Conclusion: Though nBnC HCC patients had larger tumors compared with B/C, their liver function was secured. Therefore, aggressive surgical therapy including major hepatectomy may offer good prognosis.

P-39

Reappraisal of the Benefit of Surgical Treatment in Patients with Solitary Large Hepatocellular Carcinoma

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Background: Liver resection (LR) is the first option for solitary large hepatocellular carcinoma (SL-HCC), provided that resection may be total with tumor-free margin and the patients might have an adequate liver function. However, the factors affecting the outcomes following resection remain unclear.

Objective: To evaluate risk factors for recurrence following LR for SL-HCC (>5 cm), and predictors of postrecurrence survival.

Methods: From 1994 to 2010, 182 patients underwent LR for SL-HCC and 484 were resected for solitary small HCC (SS-HCC; <5 cm). The two groups were compared with special focus on outcomes (recurrence-free survival [RFS] and overall survival [OS]). Clinicopathological factors associated with recurrence and postrecurrence survival of SL-HCC were also identified using univariate and multivariate statistical analyses.

Results: Compared with SS-HCC, SL-HCC is associated with more frequent microvascular portal invasion (41% vs 18%, $p = 0.0001$), microvascular hepatic vein invasion (22% vs 5%, $p = 0.0001$), and increased rates of satellite nodules (25% vs 7%, $p = 0.0001$). The 5-year OS (56% vs 70%; $p = 0.015$) and RFS (25% and 32%; $p = 0.005$) were better in group of SS-HCC patients. Among the 182 SL-HCC patients, recurrence was observed in 140 (77%) patients, whom early recurrence (<2 years) was found in 100 patients, whereas delayed recurrence (>2 years) was observed in 40 patients. The presence of satellite nodules (HR 4.97 [1.39–17.84]; $p = 0.014$) was identified as the only independent risk factor for recurrence. TACE as a treatment for recurrence (HR 0.544 [0.34–0.87]; $p = 0.01$) and microvascular portal invasion (HR 0.57 [0.354–0.92]; $p = 0.02$) in the resected specimen were poor prognostic factors for OS after recurrence. When SL-HCC patients were divided into four groups according to the presence of satellite nodules and microvascular portal vein invasion, LR is associated with better overall survival in SL-HCC patients without satellite nodules and microvascular portal vein invasion.

Conclusion: Surgical treatment with curative intent in SL-HCC patients is associated with high risk of early recurrence. However, SLHCC is associated with good long-term outcomes, provided that is not affected by the presence of satellite nodules and microvascular portal vein invasion.

P-40

Usefulness of a Modified Inflammation-Based Prognostic System for Predicting Postoperative Mortality of Patients Undergoing Surgery for Primary Hepatocellular Carcinoma

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Background: There is increasing evidence that the Glasgow Prognostic Score (GPS), an inflammation-based prognostic score that includes only serum C-reactive protein (CRP) and albumin, is one of the most useful scoring systems for the prognostication of cancer patients. Nevertheless, few studies have investigated the usefulness of the GPS for prediction of postoperative mortality in patients with hepatocellular carcinoma (HCC). In addition, several scoring systems are already used in the field of HCC treatment, such as the Okuda classification, Cancer of the Liver Italian Program (CLIP) score, Barcelona Clinic Liver Cancer (BCLC) classification, Japan Integrated Scoring (JIS) system and Tokyo score. Among these scoring systems, the CLIP score in particular has been accepted as a standard scoring system for such patients.

Objective: To assess the usefulness of the hGPS, we evaluated not only its predictive value based on clinical background factors, but also compared the utility of the hGPS with that of the CLIP score in patients undergoing surgery for primary HCC.

Methods: The hGPS was calculated as follows: patients with an elevated level of CRP (>0.3 mg/dl) were allocated a hGPS of 1 or 2 depending on the absence or presence of hypoalbuminemia (<3.5 g/dl), and patients without an elevation of the CRP level (≤ 0.3 mg/dl) were allocated a hGPS of 0. From among 398 HCC patients in our collected database, 300 patients (male:female = 234:66) who had undergone elective surgery for primary HCC were enrolled. Uni- and multivariate analysis were performed to investigate the most significant clinical background factors which were associated with postoperative survival. Kaplan-Meier analysis and log rank test were used to evaluate the overall survival curves for the two scoring systems.

Results: The hGPS divided patients into three independent groups, and that a hGPS of 2 predicted a higher mortality rate ($P < 0.001$) than a hGPS of 0 or 1. The results of univariate analyses demonstrated that number of HCCs ($1/\geq 2$) (odds ratio, 1.898; 95% C.I., 1.113–3.237; $P = 0.019$), CRP (odds ratio, 1.536; 95% C.I., 1.154–2.044; $P = 0.003$), AST (odds ratio, 1.019; 95% C.I., 1.005–1.033; $P = 0.006$), PIVKA-II (odds ratio, 1.000; 95% C.I., 1.000–1.000; $P = 0.039$), CLIP score (0, $1/\geq 2$) (odds ratio, 1.861; 95% C.I., 1.098–3.155; $P = 0.021$) and hGPS (0, $1/2$) (odds ratio, 2.412; 95% C.I., 1.238–4.699; $P = 0.010$) were associated with postoperative survival. Comparative analysis using these two factors showed that the hGPS was predictively superior to the CLIP score.

Conclusions: The hGPS is able to divide patients undergoing surgery for primary HCC into three independent groups, and is considered to be an important factor predictive of post-operative survival in such patients.

P-41

Lead Time and Survival Benefit in the Treatment of Early Hepatocellular Carcinoma

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Background: Early treatment has been recommended for hepatocellular carcinoma (HCC) due to its high cure rate. However, previously reported survival benefits of treating early HCC may have been overestimated because of lead time bias; therefore, potential benefits of treating early HCC should be objectively reevaluated.

Methods: Early HCC was defined as a well-differentiated cancer containing Glisson's triad (carcinoma in situ). To evaluate whether early treatment prolonged survival, overall survival after curative liver resection was compared between patients with early HCC and those with overt HCC smaller than 2 cm. To calculate lead time and survival benefit of liver resection, the survival of treated patients was compared with that of patients with early and overt HCCs who received no treatments.

Findings: After curative liver resection, the median survival of 46 patients with early HCC (8.8 years, 95% CI 7.2–11.2) was significantly longer than that of 202 patients with overt HCC (6.8 years, 6.2–8.3; $p = 0.025$). The prolongation of survival time associated with resection of early HCC, calculated as the difference in the areas under the survival curves, was 34.7 (95% CI 11.2–58.1) months. On the other hand, comparing liver resection and natural history, the survival benefits of surgery for 12 patients with early and 16 patients with overt HCCs without anticancer treatments were 74.7 (95% CI 51.9–97.4) and 73.4 (57.9–88.9) months, respectively. Consequently, the lead time and survival benefit with resection for early HCC were estimated as 33.4 (95% CI: 18.9–47.8) and 1.3 (–22.1–24.7) months, respectively.

Conclusion: The survival benefit of resection for early HCC is negligible because of lead time, and early HCC is therefore not a target lesion for surgery.